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BRITISH MEDICAL JOURNAL

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INCIDENCE OF LEUKAEMIA AFTER EXPOSURE TO DIAGNOSTIC RADIATION IN UTERO

BY

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Interest in the effects of small doses of ionizing radiations has focused attention on the possibility that doses of *x* rays such as are used in medical diagnostic radiology may on occasion be carcinogenic. Little direct evidence is available, since the effect (if it exists) is small, and to detect it very large numbers of subjects need to be studied. Mostly the evidence relates to the special case of the foetus irradiated during examination of the mother's abdomen or pelvis, and it has been obtained by retrospective inquiry into the history of her pregnancy after the child's death was known to have occurred.

The most extensive data are those published by Stewart and her colleagues at Oxford (Stewart, Webb, Giles, and Hewitt, 1956; Stewart, Webb, and Hewitt, 1958). In their study, histories were obtained from mothers whose children had died of malignant disease throughout England and Wales during the period 1953–6, and the results were compared with those obtained from a control group of mothers whose children were still alive. It was concluded that children who were exposed *in utero* to pelvimetry, or to another similar procedure, had approximately double the normal risk of dying from cancer before the age of 10 years.

In the present study, data have been obtained by a different technique. Women who were irradiated during pregnancy have been identified in the records of the radiological departments of selected hospitals and the subsequent deaths from leukaemia of the children of these pregnancies have then been discovered. The observed mortality from leukaemia has been compared with that expected on the basis of the national mortality rates. With the technique employed it was possible to study only leukaemia, and no evidence has been obtained about other types of cancer.

The Children Studied

Eight hospitals were selected, four of which served most of Edinburgh and four a compact area in North-west London. With the co-operation of the radiological departments, lists were compiled of all those women known to have been exposed, between 1945 and 1956, to diagnostic *x*-ray examination of the pelvis or abdomen during pregnancy. The great majority of these women were delivered in the same hospital, and information was obtained from the maternity department about the mother's address, the date of birth and sex of the child, and whether the child was born alive or dead. It was possible to obtain the same information for a small number of these women who (1) were found to have been delivered at another of the hospitals participating in the inquiry (or at another associated hospital), or (2) were delivered at home, but for whom out-patient records of delivery were readily available. Women whose maternity records were not thus available were excluded from the study. The great majority of these women were under the care of general practitioners or were private patients. The numbers in the various categories are shown in Table I.

TABLE I.—*Number of Women who Received Abdominal or Pelvic Irradiation During Pregnancy and Proportion for Whom Maternity Records were Available*

Maternity Records	Irradiated Women	
	No.	%
Available:		
Delivered in same hospital	38,114	87·1
,, ,, other hospital ..	351	0·8
,, at home	1,122	2·6
Not available	4,155	9·5
Total ..	43,742	100·0

In nearly all cases the information provided by the hospital enabled the registration of the child's birth to be identified in either the local or the central Register of Births. These registers then provided information about the first names of the child and the first names and the occupation of the father. The numbers of children for whom full records were obtained in this way are shown in Table II. No attempt was made to trace the

TABLE II.—*Number of Children Known to Have Been Irradiated in utero and Proportion for Whom Adequate Records were Obtained*

Records of Child	No. of Children			Total Children	
	Male	Female	Sex not Recorded	No.	%
Adequate records:					
Aborted	75	89	349	513	1·2
Stillborn	979	930	90	1,999	4·8
Liveborn	20,982	18,174	10	39,166	93·6
Inadequate records:					
Liveborn	76	70	2	148	0·4
Total ..	22,112	19,263	451	41,826	100·0

registration entries of stillborn children or of children who were known to have died in hospital, as in these cases the hospital records themselves provided all the necessary information.

The liveborn children whose sex was not recorded are known to have died in hospital in the neonatal period, so that further follow-up of these was not needed. The very few liveborn children for whom adequate records were not obtained may have been registered in districts other than those in which the hospital or the recorded address of the mother was situated, and their records could not be identified in the Central Register because, in many cases, there were too many entries that conceivably might have related to them. A few may have been missed because of a change of name at registration.

Information about the date and type of the mother's *x*-ray examination was obtained from the radiological records. All examinations directed at the mother's abdomen or pelvis were recorded if they had been made within nine calendar months of the date of delivery. On the basis of this information the women were classified into six categories according to the number and type of *x*-ray examinations to which they were exposed. The numbers of children born alive to women in each category, for whom full birth data were obtained, are shown in Table III.

TABLE III.—*Numbers of Liveborn Children Exposed to Various Types of Radiographic Examination in utero*

Exposure Category	No. of Liveborn Children		
	Male	Female	Total
A. Pelvimetry on one occasion only ..	7,864	6,900	14,768*
B. ,, ,, ,, plus additional exposure	2,487	2,072	4,561*
C. Simple abdominal radiography on one occasion only	8,921	7,659	16,584*
D. Simple abdominal radiography on one occasion plus additional exposure other than from pelvimetry	1,149	1,017	2,166
E. Intravenous pyelography	291	262	553
F. Miscellaneous	270	264	534
Total ..	20,982	18,174	39,166*

* For 10 children the sex was not recorded—4 each in categories A and C, and 2 in category B.

Identification of Leukaemia Deaths

The task of following up nearly 40,000 children until the age of 14 years to discover how many had died would have been extremely laborious. It was relatively simple, however, to discover how many had died of leukaemia, since we possessed copies of the death entries of all persons who had died of leukaemia in Great Britain from January 1, 1945, to December 31, 1958, which had been provided by the Registrars-General of England and Wales and of Scotland for the purposes of another inquiry. All that had to be done was to check the names of the children who had been irradiated against the names of the children who had died of leukaemia. If the child's first names and the first name of the father were alike on the two lists this was regarded as presumptive evidence that the irradiated child had died of leukaemia. The identity was, however, not considered to be established unless the occupation of the father was also alike and the addresses given at the time of birth and of death were the same. In all other circumstances—namely, of a lesser degree of similarity—inquiries were made from the hospital in which the child had died from leukaemia, or from the doctor who certified the death, about the date of birth of the child and the first names of the mother.

Calculation of the Expected Mortality

The mortality from leukaemia in childhood varies sharply with sex and age, and it also varied somewhat at each age during the period under investigation. We therefore had to estimate the number of children of each sex exposed to risk of death at each year of age during each of the years between 1945 and 1958. For this purpose children born in each calendar year were regarded as having been born at the mid-point of the year, and the numbers reaching each successive age were obtained by subtracting the numbers estimated to have been lost to the study during the course of the year. Since the identification of the children who died of leukaemia depended on the identification of the names of the child and of the parents given on the birth certificate, it is clear that adopted children would be liable to escape identification. All adopted children were therefore regarded as having been lost to the inquiry.

For children aged 0 years the loss rate was determined by adding the adoption rate to the infant mortality rate and the number of children of each sex lost to the study in the first year of life was then estimated by multiplying the number of entrants by this loss rate. For subsequent years the loss rate was obtained by adding the adoption rate to the corresponding age-specific death rate and the losses at each year of age were calculated by multiplying the loss rate by the average number of children estimated to have been alive throughout that year of life. For example, there were 916 living male children who were born in 1950 in the four London hospitals to mothers whose abdomen or pelvis was known to have been examined radiographically during the pregnancy. The male loss rate in the first year of life was 40.4 per 1,000 liveborn children (male infant mortality rate, 33.6, and male adoption rate at age 0–1 year, 6.8 per 1,000 liveborn children), so that the number of boys who reached the age of 1 year is calculated to be $916 - \frac{40.4}{1000} \times 916$—i.e., 879.0. The death rate and the adoption rate for boys aged 1–2 years in 1951 were 2.6 and 1.9 per 1,000 boys, so that the loss rate in the same group during this period was 4.5 per 1,000. Since the number of boys estimated at risk halfway through the year was 879.0 less half the number of losses, the total number of losses in the year (L) is $\frac{4.5}{1000}\left(879.0 - \frac{L}{2}\right)$, hence the number of losses was 3.9 and the number of boys who reached the age of 2 years is calculated to be 875.1.

Death rates from leukaemia for each sex and for each year of life were obtained for each calendar year between 1945 and 1958 by counting the number of the relevant death certificates in our possession and relating them to the published estimates of the corresponding populations. Finally, the numbers of deaths from leukaemia that could be expected to be found in our population of children irradiated *in utero* were calculated by multiplying the child-years at risk in each sex, age, and calendar year group by the corresponding leukaemia death rates. The total number of deaths from leukaemia was obtained by summing the results for all these subgroups. Throughout the calculations the data for London and for Edinburgh were treated separately. The loss rates from death and adoption for England and Wales were, however, used for both sets of data, as sufficiently detailed data were not available for Scotland.

Results

The number of children found to have died of leukaemia in the period 1945–58 was 9; the expected number was 10.5. Details of the 9 cases are given in Table IV. The numbers of deaths observed and expected among various groups of children are shown in Table V. In each group the observed and expected numbers are closely similar. It is perhaps particularly striking that there were 4 deaths from leukaemia among the 19,329 children exposed during pelvimetry, against 5.4 expected, and that there were 5 deaths among the 16,584 children exposed only in the course of one *x*-ray examination of the mother's abdomen, against 4.3 expected. All but one of the leukaemic children were exposed to radiation during the last four weeks of intrauterine life; the exception was exposed in the last month but one. An exact calculation of the expected numbers of deaths among children exposed at various periods of intrauterine life has not been made; but data obtained for a 1% sample show that 50% of the children were exposed only in the last four weeks, 38% were first exposed in the preceding two months, 10% were first exposed in the second trimester, and 2% were first exposed in the first trimester.

TABLE IV.—*Details of Irradiation in utero for Children Discovered to have Died of Leukaemia*

Date of Exposure	Category of Exposure*	Date of Birth	Interval between Exposure and Birth (Weeks)	Sex of Child	Age at Death (Years)	Type of Leukaemia
5/7/45	C	15/7/45	1	M	2	Acute lymphatic
11/7/45	C	27/7/45	2	F	9	,,
22/3/46	C	18/4/46	3	M	11	Unspecified
7/4/48	C	24/4/48	2	M	3	Aleukaemic
26/11/48	A	16/12/48	2	M	2	Acute lymphatic
18/8/49	C	10/10/49	7	F	1	Subacute
7/10/49	A	17/10/49	1	M	6	Acute lymphatic
22/8/52	A	31/8/52	1	M	4	,, myeloid
10/11/52	A	27/11/52	2	M	3	Lymphatic

* A=Pelvimetry on one occasion only.
C=Simple abdominal radiography on one occasion only.

TABLE V.—*Comparison Between Numbers of Deaths from Leukaemia Observed and Expected Divided by Age, Sex, Type of Irradiation, and Place of Residence*

Category of Children	No. of Deaths from Leukaemia	
	Observed	Expected
Boys	7	6·2
Girls	2	4·4
Age less than 5 years	6	7·5
,, 5–13 years	3	3·0
Exposure to irradiation during pelvimetry (radiation groups A and B)	4	5·4
Exposure only to one simple *x*-ray examination (radiation group C)	5	4·3
Irradiation in Edinburgh	5	5·7
,, ,, London	4	4·8
All children	9	10·5

It is clear from these data that the leukaemia mortality within the first 14 years of life was no greater among the group of children who were known to have been irradiated *in utero* than that for all children throughout the country who were born in the same years. Moreover, the leukaemia deaths were not disproportionately concentrated among those children who can be presumed to have received the heavier dose, nor among those children who were irradiated during the first part of intrauterine life. It should, however, be noted that few children were irradiated during the first three months, so that the inquiry provides little useful information about the extent of any possible risk in this period.

An incidental finding, which may be of some interest, is that the sex ratio among the irradiated children was substantially higher than normal. The sex ratio of liveborn children, shown in Table II, was 1.15 males to 1 female, whereas both for England and Wales and for Scotland the sex ratio for the years 1945 to 1956 was 1.06 to 1. An unusually high ratio was observed separately at each of the eight hospitals—the range being from 1.09 to 1 to 1.18 to 1—and in each of the years 1945 to 1956. The ratio was lower than average for the small number of children irradiated in 1956 who were born in 1957 (147 males to 144 females); but for the other 12 years the range was from 1.12 to 1 to 1.23 to 1. The reason for this high ratio is discussed elsewhere (Court Brown, Doll, and Hill, 1960). The most likely explanation would seem to be that the risk of a complicated delivery is higher for boys than for girls. Since the threat of a complicated delivery is one of the principal reasons for radiographic examination during pregnancy, this would result in a high male:female ratio among the children of irradiated mothers. There is no evident reason why the high proportion of boys in the series should have biased the results of the present inquiry.

Discussion

Before discussing the results of this investigation we must consider whether they could have been influenced by any of several factors. First, was the technique employed adequate to identify all the cases of leukaemia that actually occurred in the population studied? This we have tested in two ways: (*a*) The records of a random sample of 50 of the children were re-examined, to see if any errors had been made in recording the names of the children or of their parents; (*b*) A random sample of 50 deaths from leukaemia was selected (excluding those which referred to children born outside the period of the study) and the birth certificates of the children concerned were sought at the General Register Offices to see if the information recorded on these birth certificates would have enabled the child to be identified in the list of leukaemia deaths.

The first test revealed no inaccuracies in the data which had been extracted from the hospital records and the birth registers. The second test showed that in 46 instances the information given on the birth certificate

was identical with that available to us in the copy of the death entry. In two instances there were minor differences in spelling which would not have resulted in any difficulty in identifying the child, had he been one of those who were studied. In one instance there was a serious difference in spelling, and in one the previous birth entry could not be traced because the child had been adopted. As already pointed out, it had been realized that cases might be missed because of adoption, and this was allowed for in calculating the number of expected deaths. The one example of a serious difference in spelling might have resulted in a failure to recognize that one of the children in our records had subsequently developed leukaemia. A small number of deaths may also have been missed because the children had emigrated, but this can hardly be more than a few per cent. of the total for children under 15 years of age. It is possible, therefore, that the technique leads to an underestimate of the true incidence of leukaemia deaths by some 2 or 3%. But even if the deficiency were as much as 10% (which is very unlikely) the observed incidence of leukaemia among the irradiated children would still not exceed the national average.

Secondly, we may consider whether the results are distorted by the use of unsuitable data to calculate the expected mortality. Certainly it would have been preferable to compare the results with those obtained from a group of children born to unirradiated mothers from the same hospitals (although mothers who need to be *x*-rayed during pregnancy must differ from those who do not require such an examination and the comparison would not be ideal). Analysis of the leukaemia mortality for England and Wales and for Scotland has, however, shown that both the London and the Edinburgh leukaemia mortality rates are substantially above average for their respective countries (Hewitt, 1955; Court Brown, Doll, Spiers, Duffy, and McHugh, 1960); moreover, the Scottish mortality has been practically identical with that recorded in England and Wales. Unless, therefore, the children born at the hospitals included in this study were differentiated in some way which would have a major effect on their leukaemia mortality from all other children born in the same two cities, the method of comparison used in the study is more likely to have shown an excess among the irradiated children than the reverse.

Thirdly, it is possible that the dose of radiation received by the children in the present study may have been less than the average amount received from irradiation of the mother during pregnancy throughout the country. The eight hospitals which co-operated in the study were all metropolitan, and five of them were recognized for the teaching of obstetrics. The safety standards during radiological examination in these hospitals may therefore have been somewhat higher than average, and our results therefore not representative.

Fourthly, the number of cases of leukaemia that were observed is small and chance factors alone may have resulted in a fairly substantial risk being overlooked. If the effect of irradiation *in utero* were to raise the incidence of leukaemia by 50% above the national average the expected number of cases in our inquiry would have been $\frac{150}{100} \times 10.5$, or 15.8. In these circumstances it would not be unreasonable to attribute to chance the fact that only nine cases were observed ($P=0.04$); but it is unlikely that the effect of irradiation could be much more. Had the effect been to double the risk, the probability of obtaining only nine observed cases (or less) would have been less than 1 in 300.

The results of this investigation may therefore be regarded as evidence that radiographic examination of the mother's abdomen during pregnancy does not induce leukaemia in the foetus, or that, if it does, the additional risk induced by the methods used in eight metropolitan hospitals is likely to be less than half the general risk to which children aged under 15 years are normally exposed throughout the country. On the other hand, we may note that there was no excess of observed deaths in those children who had been exposed to procedures likely to produce the largest irradiation dose and that no cases of leukaemia occurred among children who had been exposed in the first two trimesters of pregnancy. These results weigh against the belief that a substantial excess mortality was not observed among the irradiated children merely through the operations of chance.

The results obtained in other studies have generally been somewhat different. The first and most important of these, in regard to both size and scope, was that reported by Stewart, Webb, and Hewitt (1958). They traced and arranged an interview with the mothers of (1) 677 of the 792 children under 10 years of age who had been certified as having died of leukaemia in England and Wales during the period 1953–5, and (2) 739 of the 902 children under 10 years of age who had been certified as dying in the same period from other forms of cancer. They also arranged an interview with a control group of mothers whose children were still alive and who were matched with respect to sex and place and date of birth with the children who had died. A small part of the data was eliminated because the matched pair of mothers were interviewed by different investigators or one child was adopted, and the published results relate to a total of 1,299 pairs (in 619 of which one child had died of leukaemia). The principal results relate in the history of maternal irradiation, and are shown in Table VI.

TABLE VI.—*Frequency of Previous Radiographic Examination: Mothers of* 1,299 *Children who had Died of Cancer Compared with Mothers of* 1,299 *Living Children (After Stewart et al.,* 1958)

Period	*X*-ray Examination of					
	Abdomen			Other Part		
	No. of Mothers of Cancer Children	No. of Mothers of Control Children	Ratio	No. of Mothers of Cancer Children	No. of Mothers of Control Children	Ratio
Before marriage ..	44	26	1·69:1	335	275	1·22:1
Between marriage and relevant conception	109	121	0·90:1	213	184	1·16:1
During relevant pregnancy ..	178	93	1·91:1	117	100	1·17:1
Any period before birth of child ..	296	215	1·38:1	531	456	1·16:1

The most striking observation is that of a difference between the mothers of the children dying from cancer and the control mothers in respect of the frequency of abdominal *x*-ray examinations during the relevant pregnancy (178 to 93). The difference between the two

proportions (13.7% and 7.2%) is statistically highly significant, and it was from this difference that Stewart and her colleagues concluded that children exposed *in utero* to *x* rays were about twice as likely to die from cancer before the age of 10 years as other children.

The contrast depends, however, upon the controls being a representative sample of normal children, and it may be noted that about 40% of the children who were first chosen for this purpose could not be used, principally because they had moved away from the area in which they were born. It may well be that this has not influenced the findings, but the possibility cannot be entirely excluded. Secondly, the result might be influenced by a difference between the responses of mothers whose children were dead and of mothers whose children were still alive. That there is such a difference is suggested by the data in Table VI. In all categories of exposure, with the exception of abdominal *x*-ray exposures between marriage and the relevant conception, the mothers of children with cancer indicated more frequent radiation exposure than the control mothers. It is reasonable to suppose that the mothers of dead children, and perhaps particularly of children dead from cancer, may recall the events of pregnancy more completely than the mothers of children who are alive and well, so that the results may, to some extent, be biased by a relative under-reporting of radiation exposures by the control mothers. We should note, however, that there was some correlation between (1) the magnitude of the ratio between the numbers exposed to abdominal irradiation and the number of *x*-ray films reported to have been taken, and (2) that the ratio was highest for mothers exposed during the first few months of pregnancy. This period includes that of major foetal organogenesis, when the susceptibility to induced malformations is high. Maybe the susceptibility to leukaemia induction will also be high during the same period, although, so far as we know, this is unsupported by experimental evidence.

The results of other studies are summarized in Table VII. A survey of the radiation exposure histories of children whose deaths had been ascribed to acute leukaemia in the State of California during 1955 and 1956 was reported by Kaplan (1958). He studied also the exposure histories of the closest sib and of the child's habitual playmate, and the histories of the parents. His results were equivocal. He found that the mothers of the leukaemic children gave a history of irradiation more often while they were carrying the leukaemic child than while they were carrying the child's sib; but there was less difference between the maternal radiation exposure when the leukaemic child was compared with his closest playmate.

Polhemus and Koch (1959) obtained evidence of increased frequency of post-natal radiation exposure in children developing leukaemia, but found little indication of an excessive frequency of antenatal *x* rays. They sent questionaries by post to the families of 317 children with leukaemia who had been seen at the Children's Hospital, Los Angeles, between January, 1950, and July, 1957, but obtained satisfactory data for only 251. For controls, the same number of children were chosen of a comparable social class, age, and birthplace who had attended the same hospital for other selected conditions. Of the leukaemic children 72 had been exposed *in utero*

TABLE VII.—*Frequency of Abdominal Irradiation During Pregnancy of Mothers of Cancer Children and Mothers of Control Children: Summary of Published Data**

Reference	Cancer Children		Control Children	
	Description of Group	Proportion of Mothers who Received Abdominal Irradiation During Pregnancy	Description of Group	Proportion of Mothers who Received Abdominal Irradiation During Pregnancy
Kjeldsberg (1957)	Children with leukaemia seen at Riks-hospitalet, Oslo, 1946–56	5/55 (9·1%)	Healthy children	8/55 (14·5%)
Kaplan (1958)	Children dying of acute leukaemia in California, 1955–6	37/150 (24·7%) 34/125 (27·2%)	(a) Closest sib (b) Most habitual playmate	24/150 (16·0%) 27/125 (21·6%)
Polhemus and Koch (1959)	Children with leukaemia seen at the Children's Hospital, Los Angeles, 1950–7	72/251 (28·7%)	Children attending the Children's Hospital, Los Angeles, 1950–7 with other selected conditions	58/251 (23·1%)
Ford, *et al.* (1959)	Children dying of leukaemia under 10 years of age in Louisiana, 1951–5: (a) white (b) coloured	 20/70 (28·6%) 1/8 —	Children dying of causes other than cancer under 10 years of age in Louisiana, 1951–5: (a) white (b) coloured	 48/247 (19·4%) 8/59 —
Mac-Mahon (1958)	Children dying of cancer under 10 years of age in New York City, and born in a specified maternity hospital, 1947–57	8/114 (7·3%)	1% sample of children born in one of 11 specified maternity hospitals, 1947–57, residents of New York City only	173/2,520 (7·3%)

* Excluding data of Stewart *et al.* (1958), shown in Table VI, and the data of Murray, Heckel, and Hempelmann (1959), referred to in the text.

against 58 of the control children; for exposure to pelvimetry the relevant figures were 65 and 58. In contrast, there were substantial differences in the frequency of post-natal irradiation, particularly irradiation to the thymus in infancy (reported for 11 of the leukaemic and 2 of the control children).

Ford, Paterson, and Treuting (1959) reported the results of a survey of the radiation histories of all children under the age of 10 years certified to have died from leukaemia or some other form of cancer in Louisiana between 1951 and 1955. In this study the information was obtained from the practitioners who attended the births of the children. Data were obtained for 78 children who had died from leukaemia (including 8 negro children), 74 children dying from other forms of cancer (including 13 negro children) and 306 control children who had died from other causes. The authors found that 21/78 leukaemic children (26.9%) and 21/74 children dying from some other form of cancer (28.4%) had been exposed *in utero* to *x*-rays, whereas 56/306 control children (18.3%) had been so exposed. The data for white children, which are more suitable for comparison with British data, show that exposure to radiation *in utero* was reported by 20/70 children with leukaemia (28.6%), 20/61 children with other forms of cancer (32.8%), and 48/247 control children (19.4%). The relative risk of developing cancer after exposure compared with the risk in the absence of exposure is 1.82 to 1 (that is, 40/91 : 48/199), which is close to the ratio of 2.06 to 1 obtained by Stewart and her

colleagues. It should be noted that the American investigators also found that the ratio between the cancer and control children was highest for those who were exposed during procedures involving four or more *x*-ray films (8/152 against 5/306 or 3.2:1). The similarity of these findings to those obtained by Stewart *et al.* (1958) is striking. The techniques used were, moreover, different in some important respects though they shared the characteristic that the data were obtained from persons who could have been influenced by knowledge of the subsequent fate of the child.

Kjeldsberg (1957) investigated the 68 children with leukaemia who had attended the children's clinic of Rikshospitalet in Oslo between 1946 and 1956. Data were obtained for 55 of them, and these were compared with the data for 55 living children of the same ages. The results showed a lower incidence of exposure *in utero* for the leukaemic children (9.1%) than for the control children (14.5%). The children in the control series were, however, born at a date later than the children with leukaemia, and radiographic examinations during pregnancy are likely to have changed in frequency with the passage of time.

Murray, Heckel, and Hempelmann (1959) interviewed the mothers of 65 out of the 75 residents of one county in New York State who died of leukaemia under the age of 20 years between 1940 and 1957. Three of the mothers (4.6%) said that they had received pelvic or abdominal irradiation during the relevant pregnancy which was identical with the corresponding figure for 65 residents, matched for race, sex, age, and time of death, who had died from other causes. The relevant figures for sibs of leukaemic and control children were respectively 7/93 (7.5%) and 2/82 (2.4%).

A different type of study has been reported by McMahon (1958). He examined a 1% sample of the records of all children born alive in 11 selected maternity hospitals in New York City between 1947 and 1954. Of the 2,520 selected children 160 were excluded as the parents were not permanently resident in New York City. The hospital records of the remaining children were searched for evidence of *x*-ray examination of the mother during her pregnancy, and it was found that 173 of the children (7.3%) had been exposed *in utero*. The death certificates were then reviewed of all the children who died under the age of 10 years in New York City during the period 1947–57 and whose deaths were attributed to leukaemia or some other form of cancer. These certificates include the date of birth, so that it was possible to trace the corresponding birth certificates. From these it was discovered that 114 of the children had been born in one or other of the 11 special maternity hospitals. Reference to the hospital records showed that eight of the children (7.3%) had been exposed *in utero*. The data therefore provide no evidence for a special risk associated with diagnostic *x*-ray exposure during prenatal life. The number of cancer cases, however, is small, and a slight risk might well not have been demonstrated. It is possible that the results might have been influenced by a differential migration out of New York City between children who had been exposed and children who had not. McMahon tested this by sending a questionary to a number of mothers whose radiation history was known. Replies were received equally, irrespective of whether the women had been irradiated, but it is notable that 10 out of 37 mothers who were known to have had an abdominal *x*-ray examination during a particular pregnancy stated that they had not been examined in this way. This may perhaps be regarded as confirming the suggestion that information sought direct from mothers is likely to be of variable accuracy and that it could be influenced by knowledge of the fate of the child.

It is clear, therefore, that the existing evidence of the effect of irradiation *in utero* is conflicting. This is not surprising, since the carcinogenic effect of the doses used in diagnostic radiography is certainly not great and, with the small numbers of cases recorded in some of the studies, chance factors alone could have been sufficient to prevent its recognition. During the early part of intrauterine life the risk may be relatively high, but there is little evidence relating to this period. In the present study some 750 women were irradiated in the first three months of their pregnancy and none of the children developed leukaemia during an average follow-up of over six years, which clearly suggests no major risk even at this stage of pregnancy. For the full duration of pregnancy the magnitude of any risk from irradiation in metropolitan hospitals is unlikely to be more than 50% of that normally incurred irrespective of radiographic examination. Even a small risk of this size would imply that the foetus was a great deal more susceptible to the induction of leukaemia than the adult. Estimates of the effect of radiation in the adult have suggested that a dose of 1 rad to the whole red marrow might produce about one case of leukaemia per million persons per annum for perhaps 10 years after the exposure. Since the amount of radiation received by the foetus from irradiation of the mother's abdomen is estimated to be of the order of 1 rad and the normal annual incidence of leukaemia in England and Wales under the age of 10 years is approximately 37 per million, it would follow, with a 50% increase, that the leukaemogenic effect of irradiation on the foetus would be about 20 times as great as on the adult irrespective of the relative sizes of the target tissue. If the difference in susceptibility was much less, the effect would in all probability escape recognition. In the light, however, of all the data it would seem that an increase of leukaemia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy has not been established.

Summary

Evidence of the leukaemogenic effect on the foetus of exposure to ionizing radiations *in utero* has been sought by comparing the leukaemia mortality in a group of children whose mothers were known to have been irradiated during the relevant pregnancy with that expected from the corresponding sex-and-age specific national mortality rates. Pregnant women who received diagnostic irradiation directed towards their abdomen or pelvis between 1945 and 1956 were identified in the records of the radiological departments of eight hospitals in London and Edinburgh. Information about the date of birth and sex of the child was obtained from the corresponding maternity records. If the child left hospital alive, his full name and the first names of his father were obtained from the local register or, in a few instances, from the Central Register of Births. The children who had died of leukaemia were discovered

by comparing the children's names with the list of names of all the children who had died of leukaemia in Britain between 1945 and 1958.

Altogether information was obtained about 39,166 liveborn children whose mothers were known to have been subjected to abdominal or pelvic irradiation during their pregnancy. Among their children, nine were discovered to have died of leukaemia before the end of 1958. The expected number was estimated to be 10.5. There was no evidence of any disproportionate occurrence of leukaemia among the children who had been most heavily irradiated nor among the children who had been irradiated early in intrauterine life.

Published data on the leukaemogenic effect of irradiation *in utero* are conflicting. It is concluded that an increase of leukaemia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy is not established.

We are most grateful to the Registrars-General for England and Wales and for Scotland and to the individual registrars and local authorities who assisted us in obtaining information from the birth and death registers; to the consultant staff of the Eastern General Hospital, Elsie Inglis Memorial Hospital, Royal Infirmary and Western General Hospital, Edinburgh, and of the Central Middlesex Hospital, Hammersmith Hospital, Paddington General Hospital, and Queen Charlotte's Maternity Hospital, London, who allowed us to examine the records of their patients; to the members of the radiological and records departments of the hospitals who assisted in the extraction of the hospital data; and to Mrs. R. Ash, Miss F. Callaby, Mrs. A. Frackiewicz, Mrs. E. A. O. Gray, Miss K. Jones, Mrs. M. Kidd, and Mrs. V. Peaty, who extracted the basic data and assisted in the analysis of the results.

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During the year under review the total sum committed to research by the Mental Health Research Fund was £31,477. By March 31 this year the Fund had awarded grants to research workers of £99,844 from money contributed directly to it, besides serving as an agency for funds amounting to £33,500: a total expenditure of £133,344. One of the largest grants (£3,320) was made for a study of family patterns of psychological illness as seen in general practice and the possible treatment of such illness by a combination of social worker and general practitioner; £2,100 went to the biochemistry department of Oxford University for fundamental research into the chemical structure of certain constituents of the urine in normals and schizophrenics, and another £2,510 was given for the study of chemical changes occurring in association with mood swings in manic-depressive patients. A grant of £3,000 was made towards elucidating the response of the endocrine system to stress, and £1,632 towards clarifying the nature of the intellectual changes occurring in senile dementia. (*Annual Report, 1959–60*, Mental Health Research Fund.)

LEUKAEMIA FOLLOWING RADIOIODINE TREATMENT OF THYROTOXICOSIS

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At least 60,000 patients have been treated for thyrotoxicosis with radioiodine during the last 20 years, and it is to be expected that leukaemia will have developed fortuitously in some of these patients, particularly since this treatment is most commonly given at ages at which the natural leukaemia incidence is high.

Reports have already been published of eight cases of leukaemia in patients previously treated with radioiodine for thyrotoxicosis (Pochin *et al.*, 1956; Abbatt *et al.*, 1956; Childs, 1956; Chapman, 1956; Werner *et al.*, 1957; Blomfield *et al.*, 1959; Vetter and Höfer, 1959; Kennedy and Fish, 1959), and 10 further unpublished cases are known to have occurred. It is obviously most important (1) to assess the number of cases that would be expected to have occurred purely on a chance basis, whether radioiodine treatment had been given or not; and (2) to establish the total number of cases that have in fact occurred.

In the present report an attempt is made to deal with the first of these problems as regards the United Kingdom, by determining the numbers of thyrotoxic patients that have been treated with radioiodine in this country, with estimates of their sex and age distribution and so of the leukaemia incidence to be expected since treatment on a purely chance basis. Preliminary estimates are given for certain other countries also.

The second problem is the more difficult, since the "follow-up" of these patients after treatment is unlikely to be complete and since a previous thyrotoxicosis, successfully treated with radioiodine, may presumably not always be recorded on the death certificate of a patient dying of leukaemia. It is hoped, however, that the evaluation and discussion of the first problem may in itself help to elicit information about further cases of leukaemia which may have occurred; and a study of the characteristics of such cases might give some evidence whether all could have arisen by chance or whether some may have been induced by the radioiodine treatment.

Survey in the United Kingdom

Letters were written to all physicians or hospitals in the United Kingdom that were believed to be using radioiodine in the treatment of thyrotoxicosis, a list having been prepared of all those authorized by the Medical Research Council (1948) to receive radioiodine for this purpose. This list was checked against one including all addresses to which any consignment of radioiodine greater than 10 mc. had been issued by the Radiochemical Centre, Amersham, during the previous year. The letters asked for information of any case of leukaemia known to have occurred since such treatment, the total numbers of patients treated, the numbers treated in each particular year, and the sex and age distribution of patients at the time of treatment.

*Work undertaken on behalf of the Medical Research Council.

Replies were received to all of the letters, and gave the following information:

(*a*) No cases of leukaemia were reported other than those already published (Pochin *et al.*, 1956; Abbatt *et al.*, 1956; and Blomfield *et al.*, 1959).†

(*b*) The total numbers of patients treated were estimated in all cases. A total of 10,542 patients had been treated at the 47 centres by mid-1959 (Fig. 1), mainly in clinics dealing with substantial numbers of cases (Table I).

TABLE I

No. of patients treated	1–24	25–49	50–99	100–199	200–399	400–799	800–1,599
No. of centres	8	6	6	8	12	5	2

(*c*) Information about the numbers treated in each year was given in respect of 85% of all patients (Table II). The remaining eight centres gave total numbers and the year in which the treatment was introduced, or gave numbers individually for recent years only. In these instances, numbers were assigned to years according to proportions observed in the main sample. The patient-years since treatment were estimated by assuming that dates of treatment were uniformly distributed throughout the year of treatment; so that, for example, patients treated in 1950 were taken as having a mean period of nine years from treatment until mid-1959 (Fig. 2).

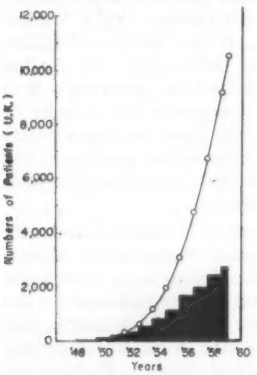

FIG. 1.—Values for the United Kingdom of total patients treated with radioiodine for thyrotoxicosis (upper curve); and numbers of new patients treated per year (lower block diagram).

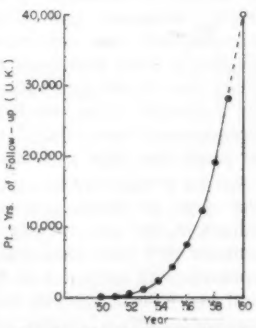

FIG. 2.—Graph illustrating the present rate of increase in the United Kingdom of the total experience of patient-years since radioiodine treatment for thyrotoxicosis.

(*d*) The age and sex of patients were given by 10-year intervals for each sex for 1,901 patients (12 centres), and by 20-year intervals for each sex for a *further* 4,638 patients (24 centres), 11 centres giving no analysis, or combining the male and female distributions.

Table III indicates the distribution observed in these groups. An estimate of the sex and age distribution in decades of all cases treated was obtained by assigning the numbers of patients in the 20-year classes of the larger sample into decades, according to the proportions observed in the smaller sample for which such data were available.

In the absence of information on the leukaemia rate in patients after treatment for thyrotoxicosis, rates for the populations of England and Wales were used, being derived from the deaths from "leukaemia and aleukaemia" (Registrar-General, 1958) as related to the numbers of persons living of the sex and ages concerned. It was found that for a population of people of the age and sex of the patients at the time of treatment with

TABLE III

Age:	–29	30–9	40–9	50–9	60–9	70–9	80–	Total	Mean Age
Females ..	11	80	374	526	444	144	9	1,588	56·2
Males ..	3	9	75	129	86	11	0	313	55·2
(12 centres)								1,901	
Females ..		397		3,337		1,674	21	5,429	
Males ..		79		710		314	7	1,110	
(36 centres)								6,539	
Percentages assumed:									
Females	0·7	5·3	21·1	29·8	19·3	6·3	0·3	82·8	54·9
Males ..	0·3	0·9	4·0	6·9	4·4	0·6	0·1	17·2	54·5
Leukaemia rates (cases per million per year):									
Females ..	15·5	21·4	37·2	53·8	97·5	136·8	148·0		
Males ..	22·0	26·4	40·5	66·5	148·5	262·6	349·0		
Product: fraction in each sex and age group multiplied by leukaemia rate									
Females ..	0·11	1·13	7·85	16·00	18·80	8·48	0·44	52·81	
Males ..	0·07	0·24	1·62	4·59	6·53	1·58	0·35	14·98	

Age-and-sex-weighted leukaemia rate (cases per million patient-years) .. .. 67·79

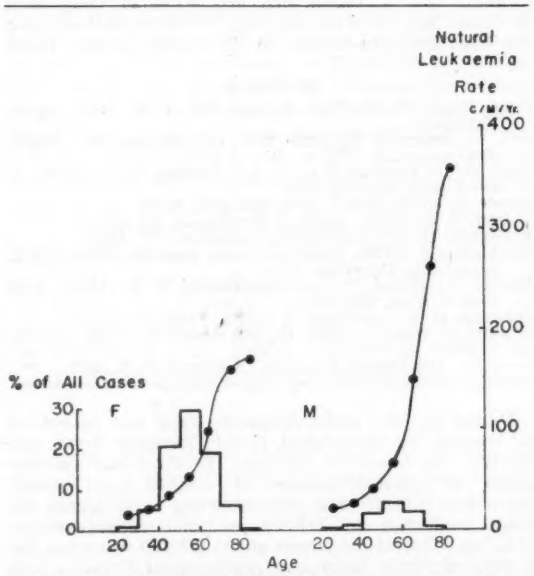

FIG. 3.—United Kingdom data on distribution of patients by sex and age groups at the time of radioiodine treatment (lower block diagrams, for female and male patients); natural leukaemia rate by age and sex (upper continuous curves, cases per million per year).

†One further case has since been reported in which lymphatic leukaemia was diagnosed four months after radioiodine treatment. In this patient, however, it was subsequently found that a blood count done one month before the dose already showed presumptive evidence of leukaemia with a white-cell count of 27,300 per c.mm., of which 90% were lymphocytes.

TABLE II

	1949	1950	1951	1952	1953	1954	1955	1956	1957	1958	Half 1959	Total
Stated Nos. of new patients treated in year (39 centres)	12	110	202	268	497	753	1,043	1,441	1,698	1,986	1,101	9,111
Estimate for whole series	12	112	206	280	532	817	1,134	1,665	1,978	2,438	1,368	10,542
Contribution to follow-up (patient-years by mid-1959)	120	1,008	1,648	1,960	3,192	4,085	4,536	4,995	3,956	2,438	342	28,280

radioiodine (Fig. 3), the incidence of leukaemia would be 67.8 cases per million per year (Table III).

With the progress of follow-up, this population will increase in mean age, and the leukaemia rate appropriate to mid-1959 is estimated as 77.8 cases per million per year, this figure being based on a population older than at the time of treatment by 2.7 years, the mean period of follow-up. With sufficient accuracy, the mean natural incidence during the period of follow-up can therefore be taken as 73 cases per million per year.

The estimate of patient-years at risk will be unduly high, since it is uncorrected for patients dying since treatment. In the absence of accurate information from complete follow-up of any groups of these patients, an approximate correction has been derived by applying the normal death rate for England and Wales to a population of the age and sex of patients at the time of treatment. On this basis, and with the observed mean follow-up of 2.7 years from treatment until mid-1959, the loss would amount to 4.5% of the estimated patient-years.‡

The number of patient-years at risk for the fortuitous occurrence of leukaemia has therefore been taken as 4.5% lower than that given in Table II, and is thus estimated as 27,000 patient-years.

When this figure is combined with an age-and-sex-weighted leukaemia incidence of 73 cases per million patient-years, it appears that 2.0 cases of leukaemia should have arisen by chance in treated patients in the United Kingdom by mid-1959.

By mid-1960 the total of 28,280 patient-years will have been increased owing to the addition of one year for each patient treated before mid-1959 (adding 10,542 patient-years) and owing to new patients treated during the year (taken as 2,800) with a mean period of half a year for each, giving an estimated total of about 40,220 patient years. This total corresponds to 13,342 patients, giving a mean follow-up of 3.0 years. On the basis already considered, the loss by natural deaths would be 5.0% and the average leukaemia rate would be 73.4 cases per million patient-years; so that a total of 2.8 cases of leukaemia would have been expected by chance by mid-1960 (Table IV).

TABLE IV

Date	Patient-Years	Average Leukaemia Rate (Cases per Million Patient-Years)	Estimated Cases
Mid-1959 ..	27,000	72·8	2·0
Mid-1960 ..	38,200	73·4	2·8

With the limited numbers involved in this country, the comparison between three cases observed and the number expected gives a very insensitive test of whether leukaemia is being induced by this treatment or whether all cases may be arising fortuitously. The expected figure of 2.8 will have a standard error of 1.7, and so would be readily consistent with any observed number from 0 to 6 and certainly with the known incidence of three cases in this country so far. These values are, of course, all dependent on the assumption that the incidence of leukaemia in treated thyrotoxicosis is the same as in the rest of the population. The present known occurrence of leukaemia after radioiodine treatment in the United Kingdom thus does not significantly exceed the number to have been expected by chance alone. But it is clearly desirable that an estimate should be made of the number of cases that would be expected over the wider area corresponding to the 18 published and unpublished cases of leukaemia which have been reported from the United States, Canada, Austria, and the United Kingdom.

‡The corresponding figure actually observed in groups of patients treated in the United States with radioiodine for thyrotoxicosis, and in which a follow-up better than 90% was maintained, has been 2.1% as based on a total sample of 1,849 patients during a mean follow-up period of 4.8 years. In a larger sample in which the dates of death were not recorded, a 3.7% death-rate occurred among treated patients in a mean follow-up period of 4.8 years as judged from a sample of 7,286 patients.

Minimum Estimate

It is comparatively easy to obtain a minimum estimate for this figure, using totals of cases known to have been treated in these countries alone, even though these totals are not comprehensive, and ignoring cases treated in all other countries. A true estimate is more difficult to derive, since full returns are not yet available even from the countries from which cases of leukaemia have been reported, and since it is clearly necessary to estimate the numbers of treatments in all countries using radioiodine therapeutically and not selectively in those in which a case of leukaemia has been observed. A minimum figure will be considered first.

With the help of Dr. H. Vetter, replies have been obtained from the three clinics dealing with the great majority of all patients treated with radioiodine in Austria. By mid-1959 461 patients had been treated, with a total of 1,303 patient-years since treatment. Table V gives the estimated total of patient-years by mid-1960, assuming a 5% correction for deaths since treatment. (An age-and-sex-specific leukaemia incidence has been calculated on the basis of U.K. rates.)

TABLE V.—*Estimates as for Mid-1960*

Country	Replies from Main Clinics	Patients Treated	Patient-Years	Leukaemia Rate (d./m./yr.)	Cases Expected by Chance
U.K. ..	All (47)	13,300	38,200	73	2·8
U.S.A. ..	Most (67)	31,400	142,000	106	15·1
Canada ..	All (34)	13,900	40,000	80	3·2
Austria ..	,, (3)	600	1,700	(73)	0·1
		59,200	221,900		21·2 (S.D. 4·6)

With the help of Dr. Sidney Werner, figures have also been sought from 80 major clinics using radioiodine therapeutically in the United States. Replies were received from 67 of these, giving totals of 29,706 patients and 142,622 patient-years by the end of 1959, the mean period of follow-up being 4.8 years. The total estimated for mid-1960, using a 10% correction for deaths during the 5.0-year mean period of follow-up, is 142,000. The age and sex distribution of patients at the time of treatment was given for 6,923 patients from 19 clinics, and the normal U.S. leukaemia rate for 1957 for such a population is equivalent to 91.2 cases per million patient-years. This value would rise to 122 cases per million patient-years at the end of a period of follow-up until mid-1960, and a mean incidence of 106 has been taken for these patients.

With the help of Dr. W. J. D. Cooke, replies have been obtained from all of the 34 clinics listed as using radioiodine therapeutically in Canada, and indicate a total of 10,298 patients and 30,892 patient-years by mid-1959. An estimate is thus obtained of 40,000 patient-years of follow-up by mid-1960 using a 5% correction for natural deaths during the 3.0-year mean

period of follow-up. The sex and age distribution of Canadian cases at the time of treatment was obtained from a sample of 2,335 patients from 16 clinics and, when combined with the natural Canadian leukaemia rate for 1958, indicated an age and sex specific rate of 72.3 at the time of treatment, corresponding to an average rate of 80 during the follow-up period.

It will be seen from Table V that, on the assumptions that have been made, a total of at least 21 cases of leukaemia would have been expected to have arisen by chance by mid-1960 in those countries alone from which cases have been reported after radioiodine treatment of thyrotoxicosis. This figure, although a minimum estimate, exceeds the cases known at present to have occurred, and would be readily consistent with any actual number of cases from 14 to 28.

Certain inaccuracies in this comparison arise because the frequency with which leukaemia has been diagnosed subsequent to radioiodine treatment has been compared with an expected frequency of *deaths* from leukaemia. In a correct comparison of deaths from this cause with expected deaths, (1) the total of diagnosed patients should be decreased by the number who had not died by the date of review (one, with three unknown, at mid-1960); but (2) it should be increased by the number of patients in whom a diagnosis had been made before treatment but who had died before the date of review. Of the three patients referred to in the footnote§ (p. 1549), one had died and two were surviving at mid-1960.

It should be emphasized also that the total of diagnosed patients is that known to me at mid-1960, but replies to letters requesting information on unpublished cases were being received mainly in the last quarter of 1959 and the first quarter of 1960. It is likely that subsequent diagnoses would have been notified by the authors of these letters (or during a discussion of these figures at the International Goitre Conference in July, 1960), and subsequent notifications were received in the first quarter of 1960, but the totals cannot, in any case, be regarded as comprehensive or as complete to the date of review.

True Estimate

The laborious task of estimating the total of all patients treated with radioiodine, and the total number of cases of leukaemia to be expected fortuitously, becomes less urgent when it is found that the present known cases are at least not in excess of the chance expectation. If it was found that more cases had occurred than are at present known, it might clearly be important to know the true figure, although the application of a normal leukaemia rate to treated thyrotoxic patients would remain quite unjustified. In different countries there is substantial variation both in the utilization of this form of treatment (Table VI) and in the age distribution and mean period of follow-up of patients treated (Table VII). It is impossible, therefore, to estimate the total number of cases of leukaemia on any basis of patient-years per million of population, although it is clear that this total will substantially exceed the minimum estimate, since many countries of large total population are known to be using radioiodine extensively.

TABLE VI

Country	Population (Millions)	Cases per Year per Million	Patient-Years per Million	Mean Follow-up (Years)
United Kingdom	52	53	730	2·8
U.S.A.	177	39	800	5·0*
Canada	17·5	170	2,300	3·0
Austria	7·0	14	240	2·9
Australia ..	10·0	51	720	2·5
France	45	67	1,100	3·3†
Italy	50	22	100	2·3*
Republic of Ireland	2·9	20	120	2·0

* Data incomplete. † Approximate figures.

The questions already discussed have dealt only with the numbers of cases observed, and two further points require consideration: the intervals between radioiodine treatment and the onset of leukaemia; and the types of leukaemia occurring.

Intervals Between Treatment and Diagnosis of Leukaemia

With the first few cases of leukaemia that occurred after treatment, it seemed that an interval of about 18 months between treatment and symptoms or diagnosis of the leukaemia was occurring with undue frequency if the development of leukaemia was fortuitous, and it seemed likely on these grounds alone that such cases might be being induced by radioiodine. With the rather fuller present experience of larger numbers of cases it becomes clear (Table VIII) that the intervals between radioiodine treatment (or first treatment with radioiodine) and the diagnosis of leukaemia are much more widely scattered, and it seems unlikely that the distribution of these time intervals alone gives any clear suggestion that cases are being induced by radioiodine. The distribution of time intervals is shown in Fig. 4.

An attempt has been made to compare this distribution with that to be expected if the onset of leukaemia were fortuitous and occurred at time-intervals after the radioiodine which corresponded only to the numbers of patients who had been under observation for the various intervals after the dose. The relative numbers of

TABLE VII.—*Age Distribution of Patients at Time of Treatment with Radioiodine*

Country	Percentage								Approx. Mean Age
	Females				Males				
	–39	40–59	60–79	80–	–39	40–59	60–79	80–	
U.K. (36)	6·1	51·0	25·6	0·3	1·2	10·9	4·8	0·1	55
U.S.A. (19)	17·2	38·8	20·7	0·4	3·5	13·0	6·2	0·2	51
Canada (17)	22·8	38·2	14·3	0·3	6·4	12·6	5·3	0·0	48
Australia*	22·6	44·6	14·8	0·0	2·8	11·8	3·2	0·0	49
Austria (1)	11·7	53·1	18·6	0·0	3·0	9·8	3·8	0·0	52
Eire (1)	6·2	53·5	28·9	0·0	0·7	7·5	3·4	0·0	55
France (3)	16·2	54·7	13·4	0·1	2·6	11·0	1·9	0·0	49
Italy (6)	24·0	42·6	8·1	0·1	5·3	18·2	1·7	0·0	46
Japan (1)	48·5	26·4	3·1	0·0	11·1	10·3	0·4	0·0	39

Figures in parentheses after the names of countries indicate the number of clinics providing data on which the age distributions are based.
* Based on a total of 653 patients "from various clinics."

patients who have passed through each of the years since treatment have been calculated from data from the U.K., U.S.A., and Canada, according to the proportion of patients treated in each year since this therapy was introduced. Fig. 4 gives a comparison between the distribution of time intervals observed between treatment and diagnosis for the 18 cases and that to be expected by chance according to the proportion of

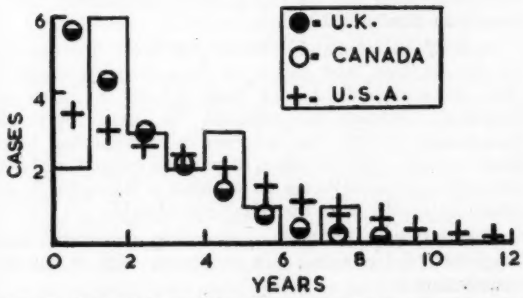

FIG. 4.—Intervals in years between radioiodine treatment and the diagnosis of leukaemia in 18 patients (block diagram) compared with incidence expected fortuitously on the basis of numbers of patients at risk during successive years after treatment (expected frequencies indicated by symbols, as calculated according to U.K., Canadian, and U.S. figures for intervals since treatment).

patients "at risk" during each of these intervals. This analysis is considerably affected by the limits chosen for the class intervals and by the small numbers of patients involved, but at least the method adopted does not appear to indicate any significant departure from a random distribution.

It may be expected, moreover, that a number of factors will introduce bias into the intervals recorded. Cases are less likely to be observed as having developed leukaemia if this occurs later than one or two years after treatment, when the patient may be lost to the thyroid clinic, since the thyrotoxicosis is likely then to be adequately controlled by the radioiodine dose. Moreover, some clinics may publish those cases developing leukaemia at time intervals after radioiodine which appear compatible with a possible induction, but may not regard it as equally necessary to publish a record of those cases developing the disease so soon after the radioiodine that it would be unlikely to have been induced by it owing to the shortness of this "latency"; and two such cases are known not to have been published for this reason. Moreover, routine blood examination before a therapeutic radioiodine dose may detect symptomless leukaemia, and cause a deficiency in cases diagnosed within the year or more after treatment. Three cases of leukaemia are known to have been detected in this way,§ and would otherwise have appeared as cases developing soon after treatment.

Types of Leukaemia

On examining the types of leukaemia that have been diagnosed after radioiodine treatment, it appears that acute forms occur in a somewhat higher proportion than would be expected in a population of the ages concerned. The types of leukaemia diagnosed are shown in Table VIII. Excluding one unascertained type, they comprise 13 acute and 4 chronic or subchronic forms, a proportion of 76% therefore having been diagnosed as acute. It is difficult to obtain a representative figure for the frequency with which leukaemia presents in an acute form at various ages for populations throughout North America and Western Europe, and the figures for England and Wales are uncertain, since the form of registration of deaths from leukaemia does not allow this proportion to be defined. On the basis of a survey (Court Brown and Doll, 1959; data for the years 1955–7), however, the proportion to be expected in England and Wales in a population of the age and sex of cases at the time of treatment would be 57% with an expectation of 9.7 acute cases amongst the 17 as compared with 13 observed. The difference between the expected and observed values is such as would be equalled or exceeded fortuitously in about 5% of trials. This point is thus suggestive and merits further examination, but is obviously not conclusive of leukaemia induction. Moreover, since the classification of leukaemia as "acute" is not based on objective criteria, and since diagnoses have been quoted without review of sections or time course, too much reliance cannot be placed on these frequencies.

§For information on these patients I am indebted to Professor Rosenheim, Dr. Sheline, and, for the case referred to in the earlier footnote,† to Dr. K. E. Halnan.

TABLE VIII

Case	Sex	Age at Time of (1st) Dose	Dose(s) (mc. ^{131}I)	Interval (Months) from (1st) Dose to			Diagnosed Type of Leukaemia	Place of Origin
				Onset of Symptoms	Diagnosis	Death		
1	F	41	7·1	19	24	29	Acute	U.K. (London)
2	F	67	17·0	18½	19	19½	,, myeloid	U.S.A. (Rochester, Minn.)
3	M	46	5·3	?	14	24	,, ,,	U.S.A. (Boston)
4	M	65	4	?	26	28	Chronic monocytic	U.S.A. (New York)
5	F	28	2·1	17	18	22	Acute ? granulocytic	U.K. (Sheffield)
6	F	50	4·9	17	17	17	,, monocytic	Austria (Vienna)
7	M	50	7·1	18	18	18	,, stem cell	U.S.A. (N. Carolina)
8	M	38	5·5	22	22½	24½	,, granulocytic	U.S.A. (Cleveland)
9	M	60	14·3	?	86	90	Chronic monocytic	U.S.A. (New York)
10	M	65	3·9	>38	43	50	Acute	U.S.A. (Iowa)
11	M	73	8·9	35	36	37	,,	Canada (Toronto)
12	M	60	28	Probably 0	3	15	Subchronic lymphatic	U.S.A. (Rochester, Minn.)
13	M	64	8·5	?	60	62	Acute	Canada (Vancouver)
14	M	?	4	?	(4 yr.)	?	Acute blast cell	U.S.A. (New York)
15	M	54	3·5	52	54	?	,, myeloblastic	U.S.A. (Columbia)
16	F	64	8	6	(1 yr.)	?	Chronic monocytic	Canada (Montreal)
17	?	?	?	?	(4 ,,)	?	?	Canada (Toronto)
18	M	58	46	32	33	42	Acute monocytic	

Note.—In the following case, a diagnosis of lymphosarcoma appeared more probable than that of leukaemia.

	F	69	12·5	?	51	?	Lymphosarcoma or aleukaemic lymphatic leukaemia	Canada (Winnipeg)

Conclusions

The present evidence, while giving no support to the idea that leukaemia is induced by the radioiodine treatment of thyrotoxicosis, neither excludes such induction nor sets any upper limit to its possible frequency. No estimates have been obtained, either of the frequency with which leukaemia has in fact occurred or of the number of cases to be expected from all countries using radioiodine therapeutically, nor has evidence been produced that the natural leukaemia rate is appropriate to patients with treated thyrotoxicosis. The only value of this report is in showing that the information at present available appears to give no indication of the induction of leukaemia.

It seems important that the quantitative aspect of this question shall be studied more widely and kept under review, not only to detect, or estimate the frequency of, any leukaemia induction that might occur, but also because the total of patient-years experienced since treatment is increasing rapidly in all countries concerned, and many more cases of leukaemia will occur fortuitously among these patients during the next few years.‖ Unless the likely scale of this increase is appreciated, there is some risk that the mere multiplication of case reports will seem to afford evidence that leukaemia is being induced by the treatment.

If all the 18 known cases of leukaemia, but no others, had been induced by radioiodine among the 60,000 patients treated in the four countries primarily considered, and perhaps 100,000 in all countries, the risk of this complication within an average time of about four years from treatment would be in the region of 0.02 to 0.03%. Even if there should prove to be an induced incidence equalling the natural rate, the level of risk (at 21.2 per 60,000 patients, or 0.035%, in four years) would still be small relative to the known risks of surgery or the prolonged use of antithyroid drugs.

If it were assumed that this treatment involves an average irradiation of blood-forming organs of 10 to 15 rads, and that one case of leukaemia was induced per year per million exposed per rad, an induction rate of 10 to 15 per million per year might be expected initially, which is equivalent to about 10 to 20% of the natural leukaemia rate at the age of treatment. Such an excess would not be detectable numerically on a total present natural expectation of, say, 40 ($\pm$6.3, S.D.) cases, although it is possible that a study of "latencies" or types of leukaemia might reveal it.

A total leukaemia risk of 20 cases per million exposed per rad during remaining life would imply, on the same basis, a risk of 0.02% from leukaemia attaching to this form of treatment. It will be appreciated, however, that no prediction of this sort can be based with any confidence on the results of other forms of radiation exposure, particularly as higher radiation doses are received during the course of this treatment locally in the liver, and, of course, in the thyroid gland itself, in which in some cases of thyrotoxicosis active lymphoid follicles with true germinal centres may be observed. It is suggested, therefore, that the numbers of cases of leukaemia following radioiodine treatment of this condition should be kept under review, however slight the risk of leukaemia induction appears likely to be.

‖ It is easy to show that, if equal numbers of new patients are treated each year, the total of patient-years will increase with the square of the time since the introduction of the treatment. If numbers treated each year are increasing linearly, the total of patient-years, and so the expected cases of fortuitous leukaemia, will increase with the cube of this time.

Summary

Leukaemia is known to have developed in 18 patients who had previously been treated with radioiodine for thyrotoxicosis, three cases having occurred in the United Kingdom, ten in the United States, four in Canada, and one in Austria.

About 60,000 thyrotoxic patients have been treated with radioiodine in these four countries alone, with an estimated total of over 220,000 patient-years since treatment until mid-1960.

Application of natural leukaemia rates appropriate to the sex, age, and nation of these patients suggests that approximately 21 (or from 14 to 28) cases of leukaemia would be expected to have occurred fortuitously among them whether radioiodine had been given or not. The numbers of patients treated in those countries in which cases of leukaemia have not been observed would raise this total considerably.

The intervals between radioiodine treatment and diagnosis of leukaemia are consistent with a chance distribution.

Of the 17 cases in which the type of leukaemia is known, 13 were diagnosed as acute, a proportion somewhat, but not strikingly, higher than that to be expected on the basis of data for England and Wales on the frequency of acute leukaemia in a normal population of corresponding age and sex.

These estimates are held to indicate that the present known records of cases in which leukaemia has followed radioiodine treatment of thyrotoxicosis gives no indication that this treatment is inducing leukaemia. At the same time they clearly do not exclude this possibility, since the total number of cases of leukaemia might greatly exceed the number at present known to have occurred.

I wish to acknowledge with appreciation the help of Dr. W. J. D. Cooke, Dr. Murray Cunningham, Dr. D. K. O'Donovan, Dr. M. Negri, Dr. D. J. Stevens, Professor M. Tubiana, Dr. H. Vetter, and Dr. Sidney Werner in the collection of information; the advice of Dr. R. Doll on presentation of the data; and the forbearance and helpfulness of many busy clinicians in a number of countries in dealing with questionaries.

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The Royal Society of Health has approved an application from the Malta Government that an Overseas Examination Board of the Society should be established in the island. The Malta Government's existing examination for health inspectors, qualifying for appointments in Malta, will become an examination of the new Board. Dr. J. GALEA, Chief Government Medical Officer of Malta, has been appointed chairman of the new Board.

LEUKAEMIA IN CHILDHOOD AFTER ANTENATAL EXPOSURE TO X RAYS

A SURVEY AT QUEEN CHARLOTTE'S HOSPITAL

BY

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The remote possibility of leukaemia or other malignant disease developing subsequently in the child has been in the minds of obstetricians using antenatal radiography ever since the publication of surveys by Dr. Alice Stewart and her co-workers. Stewart *et al.* (1956) reported that, of 269 children who died of leukaemia under the age of 10 years, 42 had been irradiated antenatally; while of 269 healthy children acting as controls, only 24 had been irradiated. Again, in 1958 Stewart *et al.* reported that direct foetal irradiation had occurred in 13.7% of 1,299 children who died of leukaemia or other malignant disease, but foetal irradiation had occurred in only 7.2% of a similar number of control children. In these two series 6% more of the children who died of leukaemia or other malignant disease had been subjected to irradiation when they were foetuses *in utero* than was the case in the control groups. Because 87% of the leukaemic children were not irradiated and 7% of the control children were irradiated but did not get leukaemia, the greatest possible proportion of children whose leukaemia could be due to antenatal irradiation is 6%. Since the incidence of leukaemia in children under the age of 10 years was 1 in 2,600 births, antenatal irradiation could not be the cause of more than 1 in 40,000 births (6% of 1 in 2,600) in Stewart's two series.

To test the validity of this argument an investigation was undertaken into the incidence of leukaemia in children who were born at Queen Charlotte's Hospital. At the time of Stewart's first paper about 25% of the babies born at Queen Charlotte's were being irradiated *in utero*. Osborn and Smith (1956) estimated that not less than 16% of pregnant women in England and Wales had an obstetric abdominal *x*-ray examination.

Thus if antenatal irradiation is a cause of leukaemia subsequently in the child there ought to be a greater incidence of the disease in children who had been born in Queen Charlotte's Hospital compared with the national average; and more leukaemic children should be found in those who had been irradiated than in those who had not.

Method

The records at Queen Charlotte's Hospital were searched for each one of 1,548 children who died of leukaemia in England and Wales before their tenth birthday during the six years 1953–8 to see if the child had been born at the hospital. Because any of the children might have been born up to 10 years before death the records had to be searched for the 16 years from the beginning of 1943 to the end of 1958, during which time there were 45,195 live births at the hospital. (Stillbirths were excluded because they could not get leukaemia.)

The names of 26 children who died of leukaemia were found similar to those born in the appropriate year at Queen Charlotte's. The birth and death certificates were then compared, but only 8 of the 26 children were in fact identical. In order to determine the extent of errors in the recording of leukaemic deaths and of births and in the method of searching, 50 test names of living children known to have been born at Queen Charlotte's were inserted into the lists of leukaemic deaths. These names were unknown to the searchers and were typed at the same time as the lists of deaths, so that there was no way of identifying them. They found 40 test names out of 50, and therefore the number of leukaemic deaths, 8, of those they found were born at Queen Charlotte's should be multiplied by a correction factor of 5/4 if these errors are to be taken into account.

Results

During the six years 1953–8 1,548 children died of leukaemia before their tenth birthday, and 8 of them were born at Queen Charlotte's Hospital (making allowances for errors in the method the number might be 10). If the incidence of leukaemia in the child population is known for each age-group from 1943 to 1958 it can be worked out how many leukaemic deaths of those under 10 years might be expected in 1953–8, given the number of live births in each year and making allowance for deaths from other causes. From the 45,195 live births during the 16 years 1943–58 at Queen Charlotte's Hospital the expected number of leukaemic deaths in 1953–8 is 6 or 7 (best estimate 6.6).

Expected Number of Leukaemia Deaths

Live Births 1943–58	Leukaemic Deaths, 1953–8	
	Expected No.	Actual No.
45,195	6·6	8

During the 16 years 1943–58 11,443 foetuses were exposed to antenatal irradiation; thus 25.3% of foetuses were irradiated. But of the 8 children born at the hospital who died from leukaemia, only one was irradiated; he was exposed to one erect lateral view of the abdomen near term.

In order to find out how many live births are related to the number of deaths in six years of children up to the age of 10 years a calculation has to be made. The total number of live births in 16 years (in this case 45,195) is multiplied by 6/16. This gives an average number of births for six years. The average number of live births for 6 of the 16 years 1943–58 is 16,948, and the average number of foetuses irradiated in six years is 4,291. Thus in six years 12,657 babies were born who were not irradiated (control children) and seven died of leukaemia before the age of 10 years, an incidence of 1 in 1,808. In the same period of time 4,291 irradiated babies were born and one died of leukaemia before the age of 10 years, an incidence of 1 in 4,291.

Incidence of Leukaemia

	Live Births for 6 Years	Deaths from Leukaemia	Incidence
Non-irradiated control cases ..	12,657	7	1 in 1,808
Irradiated cases	4,291	1	1 ,, 4,291
All cases	16,948	8	1 ,, 2,118

Conclusions and Summary

Although the figures obtained so far are not large enough to show a tendency for irradiation of the

foetus to cause one case of leukaemia in 40,000 births, they do show that the tendency is not very much greater. The incidence of 8 leukaemic deaths per 16,948 live births, 1 in 2,118, is slightly higher for Queen Charlotte's Hospital than for the country as a whole; but this is due to the much higher incidence of leukaemic deaths in the non-irradiated (control) group, 1 in 1,808, compared with the irradiated group, 1 in 4,291, and cannot therefore have been caused by irradiation.

I thank Dr. Alice Stewart for providing the lists of deaths from leukaemia, Dr. Rohan Williams for the figures on irradiated cases, and the Board of Governors of Queen Charlotte's and Chelsea Hospitals for secretarial aid in searching.

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PHENYLBUTAZONE AND LEUKAEMIA

A POSSIBLE ASSOCIATION

BY

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This paper reports six instances of leukaemia developing in patients who had received phenylbutazone. In the first patient there appeared to be a sequential progression from the development of an early toxic reaction to the patient's death from myeloid leukaemia. In the other five patients a history of administration of the drug was obtained in retrospect.

Case 1

This patient, a man aged 69, had complained of low back pain since 1918. Radiological examination demonstrated marked degenerative spondylitic changes in his lumbar vertebral column. He had not received any *x*-ray therapy for this.

In February, 1957, he was treated with phenylbutazone. The initial dose was 600 mg. a day, after a few days reduced to 400 mg. a day. Shortly after the treatment was begun he developed a sore throat, and two weeks later a swelling and a rash upon his legs. He was admitted to hospital after three weeks' treatment. Examination showed him to be apprehensive and in poor nutritional state, with a dry, red, glazed tongue. He had a scattered toxic erythematous rash upon his legs and feet, enlarged lymph nodes in his neck and axillae, and a palpable spleen. Blood examination showed a haemoglobin of 13.4 g./100 ml. and total W.B.C. 17,000 c.mm. (polymorphs 75%, lymphocytes 11%, monocytes 9%, eosinophils 4%, and basophils 1%). The red cells showed anisocytosis and poikilocytosis. Platelets were abundant and the lymphocytes and monocytes slightly abnormal, with pale vacuolated cytoplasm. Serum albumin was 3.3 g. and globulin 3.6 g./100 ml.

A left axillary gland was removed, and the report upon the section was: "The architecture of the gland is largely replaced by a medullary disturbance of the reticulum cells together with alteration of age of the lymphoid elements. The picture is consistent with an early reticulosis." The patient was given supportive therapy, including a high-protein diet and parenteral vitamins, and steadily improved. Three months later he was much better, and, although examination still revealed enlarged glands and a palpable spleen, these features were less prominent. His weight had increased. His haemoglobin had risen, and the total W.B.C. had fallen, but his platelet count had increased to 507,000. There were still 400 eosinophils present.

After a further five weeks he was again admitted to hospital. On this occasion he was very sick, with a generalized bullous rash, conjunctivitis, urethritis, and recurrent glossitis with mouth ulceration. He was thought to be suffering from erythema multiforme and he was again treated symptomatically. His Hb had fallen to 11.25 g./100 ml. His reticulocytes were 3.3% and his platelets had risen to 980,000. A blood film showed a neutrophilia with a shift to the left and toxic granulation. The platelets were predominately large forms. A marrow biopsy showed a normal marrow. He rapidly improved and was discharged approximately four weeks later when his Hb had risen to 12.4 g. However, he had persistent neutrophilia and eosinophilia, and his platelets remained abnormal, being plentiful and showing clumping.

Three months later he had again improved, his spleen was palpable on inspiration and his glands smaller but very firm. His haemoglobin had risen to 14 g., W.B.C. 15,000/c.mm. with 11% eosinophils, and platelets 780,000. The blood film remained abnormal. He was again admitted in January, 1958 (one year after his original treatment), when the findings were much the same, his blood showing neutrophilia and eosinophilia. The zinc turbidity had risen a little higher and a further gland was removed. The biopsy report stated: "Macroscopy: a small hard gland throughout which there are irregular deposits of hard white tissue. Microscopy: areas of caseation accompanied by chronic inflammatory and giant-cell reaction. Probably tuberculous." On this occasion his liver was palpable with a firm edge. He was discharged shortly after this and felt much improved.

He was again reviewed 17 months after his original illness, when he appeared to be again improving. His appetite was good and his weight increasing. Examination revealed that his lymphadenopathy was less, although the glands palpated remained very hard. His liver had also receded and his spleen was not palpable. Examination of his blood gave the following results: Hb, 13.6 g./100 ml.; total W.B.C. 10,700 (polymorphs 71%, lymphocytes 25%, monocytes 1%, eosinophils 3%); platelets, 510,000; E.S.R., first hour 15, second hour 37. Both polymorphs and lymphocytes were atypical, with coarse granular nuclei, and about 30% of the

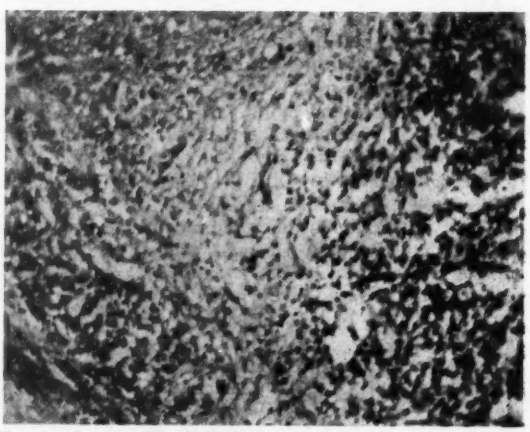

FIG. 1.—Case 1. Histological appearance of the involved glands.

polymorphs were younger forms. The blood film was consistent with early myeloid leukaemia. His serum albumin was 3.7 g. and serum globulin 3.2 g./100 ml., and zinc sulphate turbidity 10 units.

He was seen three months later, in October, 1958. A marked deterioration had taken place. He complained of recurrent swelling of his glands, weakness, and loss of weight. Examination revealed that he had a generalized lymphadenopathy. The glands were more numerous and

larger than on any previous occasion. His liver edge did not appear to have changed since examination in July, but his spleen had greatly enlarged.

Examination of his blood revealed Hb 10.9 g. His W.B.C. had risen to 88,300, with the following distribution : mature polymorphs 39%, younger forms 52%, mature lymphocytes 5%, younger lymphocytes 2%, eosinophils 1%, and atypical plasma cells 1%. The appearance of the film was that of chronic myeloid leukaemia. An *x*-ray film of the chest was clear on admission, and he was given 50 mg. of busulphan (" myleran ") ; however, six days later he developed staphylococcal bronchopneumonia, from which he died. Fig. 1 shows the histological appearance of the involved glands.

Post-mortem examination revealed staphylococcal bronchopneumonia. There was generalized glandular enlargement, the glands having a yellow appearance, with caseous foci. The bone-marrow, spleen, kidneys, and liver were extensively infiltrated by leukaemic cells. Tubercle bacilli were cultured from the enlarged glands. There was no evidence of pulmonary tuberculosis on either gross or microscopical examination.

Case 2

This patient, a man aged 67, had suffered from pulmonary tuberculosis for many years, but his chest had remained stable since a lobectomy four years prior to this admission. During this period he had not been taking any chemotherapy for tuberculosis. He had suffered from lumbar spondylitis for many years and had taken phenylbutazone intermittently over the past four years. Since his lobectomy his health had been reasonably good, and he was able to carry out a full day's work on his farm. His recent illness had started four months before admission, when he complained of increasing tiredness and dyspnoea.

Examination revealed a pale elderly man with a palpable spleen and a tender sternum. His haemoglobin was 4.4 g./100 mg., and total W.B.C. 44,400 (neutrophils 4%, lymphocytes 90%, eosinophils 1%, and smear cells 5%). The platelet count was 50,000 and large forms were present. The reticulocytes were 0.54%. The lymphocytes were predominantly younger forms with lobulated indented nuclei and nucleoli in many cells. Aspiration biopsy of his bone-marrow revealed a uniform marrow picture dominated by atypical immature lymphocytes. Myelopoiesis was scanty and no red-cell precursors were seen.

The patient was treated with transfusion, thiotepa, A.C.T.H., and prednisolone. There appeared to be a temporary improvement with thiotepa, but frank haemolysis developed and he died suddenly approximately 10 weeks after admission.

Post-mortem examination revealed the cause of death to be pulmonary oedema. His bone-marrow was pale and fatty, with little or no erythropoietic tissue. His spleen was enlarged, pale, and firm, and there was slight enlargement of lymph nodes. Microscopy revealed widespread infiltration of marrow, kidneys, liver, and spleen with lymphoblasts. Fig. 2 shows the histological appearance of the bone-marrow.

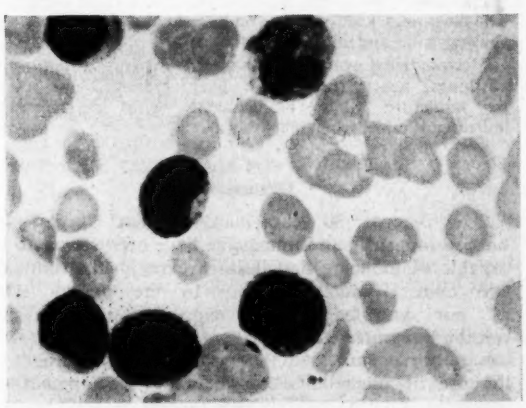

FIG. 2.—Case 2. Histological appearance of bone-marrow.

Case 3

This patient, a man aged 70, had received multiple gunshot wounds in the 1914–18 war. Since his injury he had suffered from left-sided sciatica, with wasting of his left leg. Over the last five years his sciatic pain and backache had become more severe. He stated that he had been treated with phenylbutazone tablets approximately five months before admission to hospital. In the initial period he took one to three 200-mg. tablets a day. Three months prior to admission he complained of epigastric discomfort, pains in his hips and shoulders, and anorexia. Acquaintances commented upon his pale appearance. The dosage of phenylbutazone was increased when he complained of recurrent pains, which appeared to be neuritic in type.

Examination revealed a sick-looking, pale, well-covered elderly man. He had palpable glands in his neck and axillae. His liver was enlarged and tender. His spleen was not palpable. There was evidence of degenerative cardiovascular disease.

Investigations.—Blood examination revealed Hb 6.2 g.; total W.B.C., 3,800 (polynuclears 1,520, band forms and metamyelocytes 380, lymphocytes 1,444, monocytes 380, eosinophils 38, basophils 38). Examination of the blood smear revealed 19 nucleated red cells per 100 white cells, some spherocytes, immature neutrophils, and lymphocytes. Platelets were scanty. His serum albumin was low and his gamma-globulin fraction as measured by zinc turbidity was very low. This was later confirmed by ultracentrifugation. Aspiration of bone-marrow was difficult, as there was virtually no haemopoietic tissue. Large masses of malignant cells were present, and the provisional diagnosis was malignant anaplastic tumour of unknown type. The largest axillary gland was removed and on section showed disorganization of the normal gland structure by a mass of cells. The appearance was thought to be consistent with reticulosarcoma. Kidney biopsy showed this organ to be heavily infiltrated with similar cells. A repeat blood smear revealed the presence of large lymphocyte-like cells with prominent nuclei and atypical cytoplasm.

He was thought to be suffering from leukaemia, probably subacute lymphatic in type, with marrow hypoplasia and haemolytic anaemia. He was treated with blood transfusion and " nitromin " (Yoshimoto Pharmaceutical Industries, Osaka, Japan). He showed temporary improvement and his total W.B.C. and neutrophils increased. However, his rate of red-cell destruction remained high, and a peripheral blood examination revealed an increasing content of large immature cells now considered to be either young lymphocytes or monocytes. The patient insisted upon returning to his home in the country, and failed to report for review. I later learned that he had died at home from anaemia approximately three weeks after discharge. During the last few weeks of his life he had suffered from recurrent acute bronchitis and acute otitis media.

Case 4

This patient, a man aged 80, had calcified lesions in both lungs, thought to be healed pulmonary tuberculosis. He had suffered from osteoarthritis and spondylitis for many years. In 1957 he was treated with phenylbutazone, and it was later stated that he did not tolerate the drug well. No further details are available. In December, 1958, he was noted to have an enlarged spleen at a routine examination. Examination of his blood revealed a haemoglobin of 9 g./100 ml., total W.B.C. 112,000 (polynuclears 69,440, myelocytes 29,680, monomyelocytes 1,120, myeloblasts 560, lymphocytes 3,360, monocytes 3,360, eosinophils 1,120,

basophils 3,360. He received 50 mg. of busulphan, but died suddenly 14 days later.

Post-mortem examination demonstrated chronic bronchitic changes and acute pulmonary oedema of both lungs. The tracheo-bronchial lymph nodes were enlarged. The spleen was greatly enlarged. The bone-marrow was pale and grey in appearance. Microscopy revealed infiltration of his spleen, bone-marrow, and kidneys with primitive myeloid cells. The tracheo-bronchial nodes showed myeloid infiltration and a caseous reaction consistent with tuberculous adenitis (see Fig. 3).

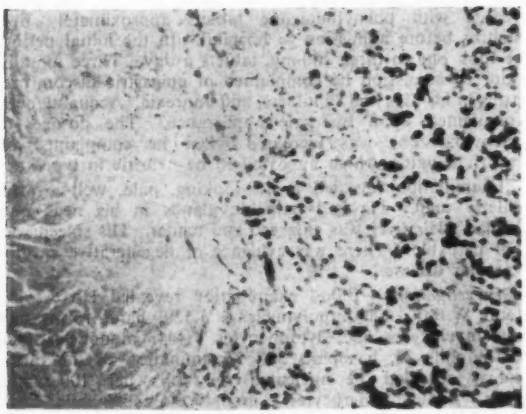

FIG. 3.—Case 4. Histological appearance of tracheo-bronchial nodes.

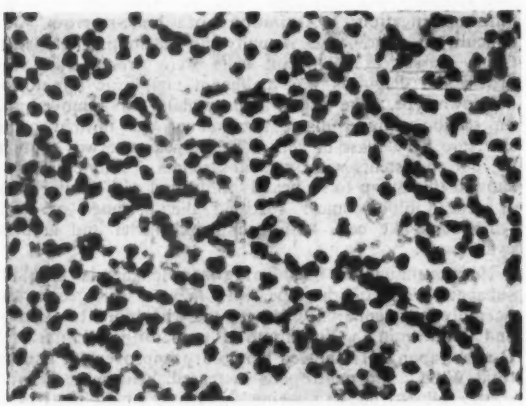

FIG. 4.—Case 5. Histological appearance of the gland.

Case 5

This patient, a man aged 66, had suffered gunshot wounds in the 1914–18 war. For nine years prior to admission he had complained of increasing pain and stiffness in his hips, and over the preceding four years he had received phenylbutazone. The initial dosage was 600 mg. a day, but this had been gradually decreased to 100 mg. a day. The patient stated that he had obtained considerable relief from the drug, and had not noticed any adverse effects. His most recent admission had been for recurrent diarrhoea, and at examination he was found to have an enlarged spleen and enlarged lymph nodes in his neck, axillae, and groins. A blood examination revealed a haemoglobin of 12.8 g./100 ml., total W.B.C. 3,450 (polynuclears 2,070, lymphocytes 1,035, monocytes 172, eosinophils 173, and platelets 190,000/c.mm. Examination of his bone-marrow did not reveal any abnormal features. An axillary lymph node was removed, microscopy revealing the tissue to be uniformly infiltrated with small round cells. These cells had invaded the gland capsule. The pattern was consistent with either lymphatic leukaemia or a lymphosarcoma. (Fig. 4 shows the histological appearance of the gland.) This patient has since been treated with small doses of tretamine with some improvement. A further gland biopsy six months after that illustrated showed an identical histological appearance.

Case 6

This patient, a man aged 63, had suffered from osteoarthritis of his left knee for many years and had received at least one course of phenylbutazone, consisting of 50 100-mg. tablets, approximately 18 months before his admission to hospital. He had also suffered from coronary heart disease with angina of effort for a number of years.

He was admitted to hospital complaining of a recent increase in the severity of his angina pectoris and severe gnawing epigastric pain. His haemoglobin was 7.9 g./100 ml., and total W.B.C. 4,200/c.mm. (neutrophils 16%, lymphocytes 76%, monocytes 7%, eosinophils 1%). The erythrocytes showed a wide variation in morphology; bizarre cells of all shapes and sizes were seen, with occasional normoblasts. The white cells appeared morphologically normal, but there were many giant forms in a normal total platelet count. This appearance was strongly suggestive of myelofibrosis. A barium-meal examination showed evidence of ulceration in the prepyloric region of the stomach, but this was not confirmed by gastroscopy. In spite of antibiotics, blood transfusion, and other supportive treatment the patient's condition continued to deteriorate and his total W.B.C. count fell further, with the gradual development of atypical myelocytes.

Examination of the bone-marrow showed a marked disturbance of both erythropoiesis and myelopoiesis. Erythropoiesis was very active, and many immature and abnormal forms, including megaloblasts, were present. Myelopoiesis was not very active, and consisted almost entirely of primitive cells. The bizarre bone-marrow picture was therefore suggestive of either an acute myeloproliferative disorder or erythroleukaemia. The patient's haemoglobin was maintained only by repeated blood transfusions. Two months after admission he developed bronchopneumonia, and was treated with antibiotics. Although his chest gradually cleared, his physical condition deteriorated rapidly. Three weeks later his peripheral blood showed a haemoglobin of 9.2 m./100 ml., and a sudden rise of white cells to 18,800 (90% neutrophils, the majority atypical younger forms). The morphology of the red blood cells had greatly improved, and there was only moderate anisocytosis and hypochromia. The blood picture at this stage was consistent with myeloid leukaemia. Six days later the patient died suddenly.

Post-mortem examination revealed evidence of a recent myocardial infarct, old coronary heart disease, and lobar pneumonia. The spleen was enlarged (260 g.) and congested. The liver and kidneys were enlarged, and the suprarenals showed wide and ill-defined cortices.

Microscopical examination showed widespread infiltration of lungs, heart, suprarenals, liver, kidneys, and spleen by immature white blood cells, with characteristics indistinguishable from myeloblasts.

Discussion

Over the past 30 years many chemical agents used both in industry and in medicine have been shown to be capable of inducing neoplasia in experimental animals and man (Haddow, 1958). In the present state of our knowledge, only circumstantial evidence can be presented to indicate whether an agent is a carcinogen or not. In these cases the association of the use of phenylbutazone and the development of leukaemia may be entirely due to chance, but the fact

that this group of cases has been observed in a relatively short period in a medical service whose clientele is largely limited to veterans of the 1914–18 and 1939–45 wars must be given some weight.

If in these patients phenylbutazone has acted as a carcinogen, then this is the result of a dose and a duration of treatment that have varied from 10 g. over a three-weeks period in Case 1 to some hundreds of grammes in four years in Case 2. In Case 1 there was a definite progression from the time of administration of the drug to the development of frank myeloid leukaemia 16 months later. It might be argued that this patient suffered from a leukaemoid reaction secondary to tuberculous lymphadenitis, but there are features which make the diagnosis of leukaemia inescapable—namely, the duration and progression of the illness, the presence of increased and abnormal platelets, and the post-mortem findings of diffuse myeloid infiltration of most body tissues. Case 6 shows similar features. The dosage of phenylbutazone was small, the period between the administration of the drug and the development of leukaemia was approximately 18 months, and the appearance of abnormal platelets antedated the development of leukaemia. If these findings were isolated no conclusion could be reached, but when the group is considered as a whole the argument develops greater weight.

Some features of this series deserve further consideration. Firstly, all patients are elderly and rather poorly nourished. (The population of this hospital is largely male.) Secondly, tuberculosis occurred in three of these patients. In this regard I have previously noted the occurrence of tuberculosis in patients suffering from other haematological reactions after the administration of phenylbutazone. There does not seem to be any consistent pattern in this association. Thus in Case 1 the tuberculous adenitis appears to have reached its maximum activity during the year after the initial reaction to the drug, and to be becoming quiescent when leukaemia supervened. Case 2 was a known sufferer from pulmonary tuberculosis, but there is no evidence that administration of the drug caused any alteration in his pulmonary disease. Case 4 had old pulmonary tuberculosis, and, at necropsy, foci strongly suggestive of active tuberculosis were found in the tracheo-bronchial lymph nodes.

There have been several cases in the literature in which caseous reaction has been reported to follow the administration of phenylbutazone (MacCarthy and Jackson, 1955). The histological appearance of the lesions described in these papers is strongly suggestive of tuberculosis, and technical difficulties may well explain failure to demonstrate the organisms. It may be of some significance that, recently, extracts of tubercle bacilli have been shown to have an adjuvant effect in the production of many reactions, many of these of the auto-immune type (*British Medical Journal*, 1959).

In Cases 3 and 5 there was an associated hypogammaglobulinaemia. In my experience this type of disturbance is not uncommon in reticuloses. Cases 3 and 6 had several severe acute pyogenic infections during the last weeks of their lives.

A third feature is the bizarre clinical and histological picture present in these cases. In the more acute cases the peripheral blood film and bone-marrow morphology were atypical and difficult to interpret. Bone-marrow aplasia and haemolysis were associated with the illness in at least three out of the six cases. In the first four cases and the last one the leukaemic phase was extremely short, and treatment apparently produced, at the best, transitory improvement.

Court Brown and Doll (1959) have demonstrated an apparent increase in the incidence of leukaemia. The information gathered by them may be interpreted in different ways, but it seems reasonable to conclude that there has been an increase in the acute leukaemias, particularly in elderly persons. They suggest that radiation has played an important part in this change. There had not been any exposure to *x*-ray therapy in the present series. Perhaps more attention might be paid to the role of chemical agents. In this regard a remark of Rupert Willis (1948) is worth noting: "All drugs or other substances known to be capable of causing agranulocytosis should also be suspected as a possible cause of leukaemia."

Summary

Six cases of leukaemia occurring in elderly males are reported.

In all of these patients there was a history of the recent administration of phenylbutazone.

In one of the cases there appears to have been a strong sequential relationship between the drug and the disease, starting from an early typical toxic reaction to the drug and terminating 18 months later in death from myeloid leukaemia.

I thank Dr. A. Bardsley, specialist medical officer of the Repatriation Department, for referring Case 5 to me and for his assistance in preparing this paper, and I am grateful to the chairman of the Repatriation Commission for permission to publish it.

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The International Brain Research Organization, founded to co-ordinate results and facilitate training and research in this branch of science, has been established recently as a result of a four-day meeting at Unesco House in Paris. The meeting brought together 18 scientists from 12 countries as members of a central committee representing the seven principal branches of neurology: neuroanatomy, neuroendocrinology, neurochemistry, neuropharmacology, neurophysiology, the behavioural sciences, and biophysics. The meeting was convened on behalf of Unesco by the Council for International Organizations of the Medical Sciences, and committee members came from Argentina, Australia, Canada, France, the German Federal Republic, Italy, Norway, Poland, Sweden, the United Kingdom, the U.S.S.R., and the United States. The meeting adopted the statutes of this new international non-governmental organization and elected its executive committee. Professor H. H. Jasper, of Montreal, neurophysiologist, was chosen as executive secretary of the committee, which included Dr. P. K. Anokhin (U.S.S.R.), Dr. A. Fessard (France), Professor G. W. Harris, F.R.S. (United Kingdom), Dr. H. W. Magoun (U.S.A.), Dr. Giuseppe Moruzzi (Italy), while Dr. Heinrich Waelsch (U.S.A.), Dr. D. Bovet (Italy), Dr. A. Brodal (Norway), and Dr. W. A. Rosenblith (U.S.A.) were chosen as alternative members of the committee.

LEUKAEMIA AND FOETAL HAEMOGLOBIN: A CASE STUDY

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The persistence of foetal haemoglobin formation after infancy has been taken to indicate an anaemic state dating from early life and is most commonly found in association with the hereditary haemoglobinopathies, though it may also occur to a less extent in congenital spherocytic anaemia (Lehmann, 1959). An extensive search has been made in many other types of anaemia, but only slight increases in foetal haemoglobin (Hb-F) have been found (White and Beaven, 1959). A considerable increase (10–20%) was, however, found by Beaven and White (1953) in a child aged 3 years with leukaemia.

We wish to record a similar finding in an adolescent girl with acute myeloid leukaemia because of the interesting possibilities which this observation raises in relation to the aetiology and diagnosis of the condition.

Case History

The patient, a schoolgirl aged 12 years, had no complaints of ill-health, but her mother had noticed the child's increasing pallor over the previous year, and eventually asked her practitioner for a "blood test." The girl was then referred to the medical unit for further investigation of anaemia. On admission she gave the additional history of unilateral epistaxis over the previous five years which had stopped after cautery six months before she was first seen by us. There was no complaint of lassitude, weakness, or dyspnoea, jaundice had not been noticed, and she had been able to continue her usual school activities. She had a normal appetite, and had gained weight and grown appreciably in the year before her admission to hospital. Her menarche was at 11 years and the menses were normal.

Past History.—A year before her present admission she had attended a hospital and had had a general anaesthetic for incision of an axillary boil.

Family History.—There was no family history of anaemia or jaundice; her parents were healthy and both were English, but one paternal grandparent was Swiss. A brother and a sister were well, but another brother had died in infancy of an unknown cause.

On examination she was seen to be a well-built girl, advanced for her age both physically and mentally. She was slightly jaundiced and moderately anaemic. There was no lymphadenopathy, the liver was not palpable, but the tip of the spleen could just be felt.

Haematological Investigations

Blood Picture.—Red cells, 2,400,000/c.mm.; haemoglobin, 7.8 g./100 ml.; P.C.V., 29%; M.C.H.C., 28%; M.C.V., 120 cubic microns; reticulocytes, 6.5%; nucleated red cells, 450/c.mm.; leucocytes, 6,100/c.mm. (neutrophils 47%, lymphocytes, 42%, monocytes 1%, leucoblasts 5%, myelocytes 2%, metamyelocytes 3%); platelets, 164,000/c.mm. The stained film showed macrocytosis, marked anisocytosis, and polychromasia of the red cells, but there were no target cells, spherocytes, or elliptocytes. Her blood group was O CDe/cde.

Bone Marrow.—There was marked hyperplasia of the sternal marrow, particularly of the erythroid series, resulting in a reduction of the myeloid:erythroid ratio, and there was no excess of myeloblasts. Erythropoiesis appeared to be mainly normoblastic in type although some of the cells showed features suggestive of late megaloblasts. There were no features such as atypical erythroblasts to suggest erythraemic myelosis.

Other Findings.—The direct antiglobulin (Coombs) test gave a positive reaction which, however, was very weak and appeared to be of the non-gamma-globulin type. The osmotic fragility of the red cells was normal. The serum bilirubin concentration was 3.4 mg./100 ml.; serum protein 6.6 g./100 ml., with a normal electrophoretic pattern; thymol turbidity 5 units; serum alkaline phosphatase 8.1 K-A units; urobilinogen was present in excess in the urine, though no bile salts or pigments were present; serum iron 262 μg./100 ml. The serum vitamin B_{12} was 867 $\mu\mu$g./ml. The significance of this figure, which is above the upper limit of normal for the method in this laboratory (Kilpatrick *et al.*, 1960), is uncertain because the patient had taken an oral preparation of vitamin B_{12} before coming under our care.

From these results the patient seemed to have a haemolytic type of anaemia of unknown aetiology, and despite her nationality the possibility of a haemoglobinopathy was raised.

Estimation of the foetal haemoglobin (Hb-F) using the alkali-denaturation method of Singer *et al.* (1951) showed this to be increased to 19%, and its electrophoretic mobility was consistent with that of Hb-F, in that it could not be completely resolved from Hb-A. I was, however, possible to identify the abnormal haemoglobin as Hb-F immunologically by a precipitin reaction with an anti-Hb-F rabbit serum. There was no increase in $Hb\text{-}A_2$ and no other abnormal haemoglobins were found (Lehmann, personal communication). The normal physical development of the patient, however, made the diagnosis of a long-standing anaemia extremely unlikely. The haemoglobin of both parents showed a normal electrophoretic pattern and their Hb-F concentrations were less than 1%.

Radioactive Isotope Studies

A series of radioactive isotope studies were made during the third week of her admission in order to study red-cell survival and erythropoietic activity in this patient.

Methods.—The red cells were labelled with approximately 75μ of $C^{51}Cr$ as sodium chromate by a modification of the established method (Wetherley-Mein *et al.*, 1958), and assessment of red-cell destruction was expressed as "percentage chromium loss per day" as described by these authors. With a tracer dose of ^{59}Fe (approximately 10 μc.) assessment of erythropoiesis was based on surface-counting patterns and iron utilization in the week following the injection of the isotope (Wetherley-Mein *et al.*, 1956).

Because measurements were carried out almost simultaneously a double isotope-counting technique was used (Wetherley-Mein *et al.*, 1958).

Results.—In the first study the patient's own red cells were labelled with ^{51}Cr. There was a 4.6% ^{51}Cr loss per day and the ^{59}Fe surface-counting study showed considerable deviation of the isotope to the liver and spleen. The plasma half-clearance time for iron was normal (105 minutes), but the iron utilization was only 25% on the sixth day. In the second study the patient's red cells were tagged with ^{51}Cr and injected into a recipient—a man with a bronchogenic carcinoma who died before the cell-survival study could be completed. A 5.4% ^{51}Cr loss per day was demonstrated over a five-day period. At a later date red cells of appropriate

blood group from a normal healthy donor were tagged with ^{51}Cr and injected into the patient. In this instance a ^{51}Cr loss per day of only 1.3% was found.

Progress and Treatment

Folic-acid deficiency may occur in haemolytic anaemias (Chanarin *et al.*, 1959), and because there were cells in the marrow which resembled late megaloblasts folic acid was given for 10 days. There was no reticulocyte response (see

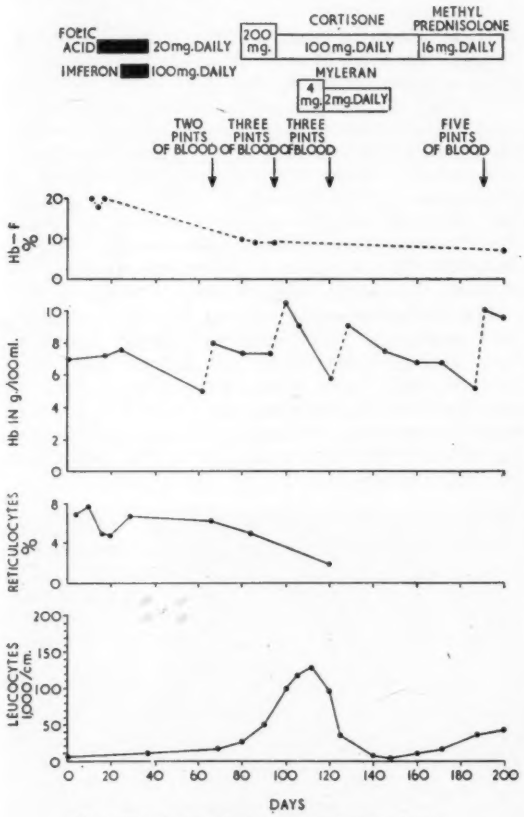

Chart showing progress and treatment of case.

Chart) and a second marrow preparation at the end of this period showed no change. The M.C.H.C. rose from 28% to normal (33%) after one week of parenteral iron.

During the next month the haemoglobin fell to 5 g./100 ml. and the platelet count to 65,000/c.mm., while the leucocyte count had risen to 15,600/c.mm. (neutrophil polymorphs 26%, lymphocytes 16%, monocytes 17%, neutrophil metamyelocytes 6%, neutrophil myelocytes 8%, premyelocytes 4%, leucoblasts 13%, normoblasts 8%, unclassified 2%). The leucocyte alkaline phosphatase was equivalent to 3.7 mg. of phenol liberated/10^{10} W.B.C./quarter-hour incubation as measured by the method of Valentine and Beck (1951) modified by Withey (personal communication). This low result is consistent with a diagnosis of leukaemia. These findings demonstrate that the haemolytic anaemia with which she had presented was probably symptomatic of leukaemia. The direct antiglobulin reaction had become more strongly positive by this time, but an antibody could not be eluted from the erythrocytes.

Cortisone was then given (200 mg./day) in the hope that it might slow down the rate of red-cell destruction, but it can be seen from the Chart that there was no striking improvement as measured by the rate of fall of haemoglobin, and that there was a marked rise in the leucocyte count due mainly to primitive cells, the blast cells rising to 33% of the total. This deterioration may possibly have been coincidental, but it would seem to bear out the suggestion (Wintrobe, 1956) that cortisone may have an adverse effect on the course of an acute myeloid leukaemia. It can also be seen from the Chart that the foetal haemoglobin concentration remained unchanged during the first weeks after cortisone therapy. The subsequent decrease in Hb-F concentration was presumably due to destruction of red cells with little or no further red-cell formation and to dilution by transfused blood.

Treatment with busulphan ("myleran") 4 mg./day was started, and this was followed by a marked reduction in the number of circulating leucocytes during the next month. At this time the patient developed an acute arthritis affecting the right shoulder and left elbow which responded rapidly to colchicine. Although association of gout with rapid leucocyte destruction during remissions in leukaemia is recognized (Hickling, 1953), her serum uric acid was only 3.1 mg./100 ml. at this time. A second remission was induced by busulphan, but, at the time of writing, 10 months after she was first seen, the total leucocyte count in the peripheral blood was 38,000, of which 30% were blast cells.

Discussion

Although it is probable that the haemolytic process had been present in our patient for the best part of a year, there was no evidence when she was first seen that this was secondary to leukaemia. The leucoblasts in the peripheral blood were considered to be in keeping with a haemolytic process in a young person and the marrow appearances were consistent with this view. The diagnosis was further confused by the finding of 19% Hb-F in the blood, which suggested that the anaemia was congenital, and a diagnosis of a haemoglobinopathy such as thalassaemia was considered until the leukaemic nature of the disease became apparent.

The patient's red cells had a diminished survival, as measured at 24-hourly intervals after injection of ^{51}Cr-tagged cells both in her own circulation and when transfused to a recipient. An intracellular defect of the red cells is therefore postulated rather than an antibody-antigen mechanism in which one would expect the red-cell survival to be substantially normal in a normal recipient after an initial increased rate of destruction during the first five hours after injection (Mollison, 1959). This interpretation is supported by the finding of a normal survival rate when cells from a healthy donor were injected into the patient, though the possibility of a blood-group-specific antibody acting on the patient's cells cannot be excluded. The intracellular defect in the red cells could be part of the leukaemic process, but it is possible that, after infancy, red cells containing Hb-F have a shorter life-span than cells containing adult haemoglobin.

The chief point of interest in this case is undoubtedly the presence of large quantities of foetal haemoglobin. Production of foetal haemoglobin is under a different genetic control from Hb-A, and its presence in our patient must have been due either to a genetic abnormality recently acquired by her marrow cells or to a congenital genetic abnormality with persistence of Hb-F since birth. The frequency with which chromosome abnormalities were found in acute leukaemia led Baikie *et al.* (1959) to the hypothesis that this disease is related to changes in the genetic material in the marrow cells. We suggest that the presence of Hb-F in our patient is likewise a reflection of a

chromosome abnormality. The presence of Hb-F could have been caused by an alteration in the genetic pattern of the marrow cells occurring either at the time of onset of the leukaemia or subsequently. There is, however, the other possibility that a pre-leukaemic chromosomal abnormality which caused persistence of Hb-F had been present from early life.

It will be interesting to discover whether this association of Hb-F and leukaemia is fortuitous or whether it will prove to be an important observation from an aetiological as well as from a diagnostic point of view.

Summary

The case of a girl with leukaemia presenting as haemolytic anaemia associated with 19% foetal haemoglobin is described. Evidence suggestive of a defect in her red cells was found.

The possible significance of these findings is discussed in relation to the genetic hypothesis for the aetiology of leukaemia.

We wish to acknowledge our indebtedness to Professor H. Scarborough and Professor J. Gough for their advice and encouragement, to Dr. H. Lehmann for measurement of Hb A_2, and to Mr. R. G. Wood for his help with the isotope studies.

ADDENDUM.—Marrow and peripheral blood have now been cultured from this patient during a second remission induced by busulphan. There were no morphological abnormalities in the chromosomes of cells cultured from the peripheral blood, and the chromosome number was 46. The chromosomes of the few intact marrow cells which could be examined in detail were morphologically normal. This investigation was done by Dr. C. M. Clarke and Mr. G. Breckon, of the M.R.C. Microbiological Research Unit at Harwell, to whom we are greatly indebted.

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This year a home-printer's course for instructing spastics in the printing of Christmas cards was organized with the help of a retired master printer. It was designed to enable those who were too severely handicapped to be placed either in open industry or sheltered employment to earn money by working at home. As most of those who attended the course were too handicapped to handle small type a system was devised whereby all printing could be done by means of printers' blocks. The course was sponsored by the National Spastics Society's employment department. Christmas cards printed by spastics can be obtained from Sundew Cards, 32 The Mall, Ealing, London W.5.

DYSPHAGIA LUSORIA PRESENTING AS A SUPERIOR MEDIASTINAL SYNDROME

BY

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In 1787 Dr. David Bayford carried out a necropsy on a woman who died of starvation, after having suffered from dysphagia from the age of 13 to 60. At first he could find no obvious cause for her symptoms, but ultimately his dissection led him to the discovery of an aberrant subclavian artery, which arose from the left side of the aortic arch and coursed between the oesophagus and the trachea to supply the right arm. He concluded that this anomalous vessel had pressed upon the oesophagus, causing dysphagia. He applied to this disorder the name of dysphagia lusoria, *lusus naturae*, meaning a freak of nature (Asherson, 1952).

Dysphagia lusoria in infancy signifies oesophageal compression by any congenital arterial abnormality, such as right aortic arch, any aberrant great vessel, vascular ring, double aortic arch, and right aortic arch with an aberrant left subclavian artery. In adults the term usually denotes oesophageal compression due to an aberrant right subclavian artery, this usually being the only abnormality.

Incidence

In the adult type of disorder the right subclavian artery arises from the left side of the aortic arch beyond the origin of the left subclavian artery. This vessel then courses to the right in one of three ways. It may run behind the oesophagus (80%), between the oesophagus and the trachea (15%), or in front of the trachea and oesophagus (5%) (Neuhauser, 1946). It will be seen from this that classical dysphagia lusoria as described by Bayford is probably extremely rare. Aberrant subclavian artery has been estimated to occur in about 1% of otherwise normal people. Some anatomical studies place this figure as high as 2%, but radiological studies obtain about 0.18% of positives (Palmer, 1955). The abnormality therefore is common, but the production of symptoms is very rare. I was able to find only seven references to dysphagia lusoria in the English language over the past ten years.

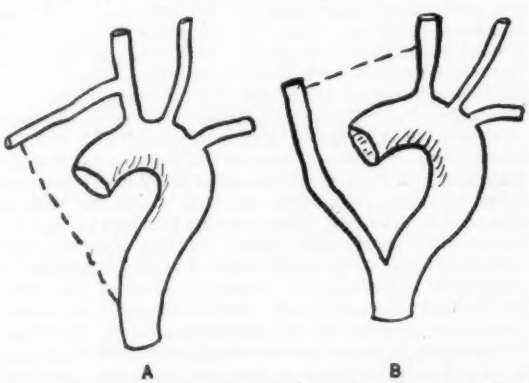

FIG. 1.—A. The caudal portion of the right aortic arch normally disappears. B. The cephalic portion disappears and the caudal part persists, forming the aberrant right subclavian artery.

If there were any point in doing so, I feel that the radiological diagnosis could be made as often as the anatomical diagnosis, using the method of subclavian-artery catheterization as described by Raphael *et al.* (1952). Symptoms are usually so mild and non-progressive that this procedure is not warranted.

FIG. 2.—Origin and course of the aberrant right subclavian artery, with the dilated diverticulum of Kommerell. Adapted from Gross (1946).

Anatomy

Embryologically, an arteria lusoria represents the persisting distal descending portion of the fourth right aortic arch, there having been obliteration of the proximal arch in reverse of the normal situation. Normally the fourth right aortic arch forms the right aortic arch, which disappears. Its persistence leads to the formation of an aberrant subclavian artery (see Fig. 1). At the origin of the abnormal vessel there may be an aneurysmal dilatation known as the diverticulum of Kommerell (see Fig. 2).

Symptomatology

The commonest and mildest symptom is a feeling of food sticking under the manubrium sterni. Regurgitation is rare, but has caused a fatality (Felson *et al.*, 1950). The dysphagia may be mild and chronic or mild and recurrent. It may become progressively worse or, as in the case described below, it may be fairly severe with acute exacerbations. Palmer (1955) mentions the symptoms of disability, fear, and fatigue, but it is difficult to see how these arise. The dysphagia is mainly for solids, but also for liquids if taken fast. There is no pain, and the swallowing-time is usually normal. In infants respiratory symptoms usually predominate; in adults, dysphagia. Certain signs have been described, but they are rare. For example, there may be inequality of the radial pulses (Copleman, 1945), and, rarely, trophic changes in the affected limb (Felson *et al.*, 1950). I have not encountered in the literature anything approaching the symptoms experienced by our patient.

Diagnosis and Treatment

Many cases of so-called globus hystericus must have been referred to psychiatrists under the mistaken impression that no organic cause existed for their symptoms. Greater awareness of the symptomatic possibilities of aberrant subclavian artery will lead to the diagnosis in an increasing number of cases, and, in fact, this disorder may come to be rather commonplace. Apart from the clinical presentation, there are four main diagnostic measures which may be employed to prove the origin of the patient's symptoms.

1. Barium swallow: If the typical appearances are encountered there is usually no need to proceed further with diagnostic measures. In the postero-anterior view, if the oesophagus contains too much barium no indentation will be seen (Fig. 3). If, however, there is merely a trace of barium present one will notice an oblique radiological defect about 0.5 cm. wide passing upwards from left to right on the posterior aspect of the oesophagus just above the aortic arch, which is usually in its normal position (Fig. 4). On the postero-lateral aspect of the oesophagus the abnormal vessel produces a typical notch (Fig. 5). If the vessel runs in front of the oesophagus a similar P.A. appearance is noted, but in this case the notching will be anterior. Should the vessel course in front of the trachea, no oesophageal defect will be encountered. In the P.A. view, above the aortic knuckle, there may be a prominence of the left mediastinal shadow of pulsatile nature, probably due to Kommerell's diverticulum (Stauffer and Pote, 1946).

2. Angiography may be employed to demonstrate the aberrant vessel, but this form of investigation carries a risk and is better avoided.

3. Oesophagoscopy may reveal the presence of a pulsatile oesophageal defect, either anteriorly or posteriorly, in about 40% of cases (Palmer, 1955).

4. The right subclavian artery may be catheterized without the injection of dye, and, in conjunction with a barium swallow, the defect can be proved to be due to an aberrant right subclavian artery.

FIG. 3 FIG. 4 FIG. 5

FIG. 3.—Oesophagus overfilled with barium. The defect is not apparent. P.A. view. FIG. 4.—Oesophagus now contains little contrast medium, and the obliquely running defect is clearly visible. FIG. 5.—Notching of the postero-lateral border of the oesophagus is evident in the left anterior oblique projection.

In infants surgical intervention usually becomes imperative, because of the serious nature of the underlying abnormalities (Gross, 1946; Gross and Neuhauser, 1951). There is no record of an adult patient having been operated on. Palmer described 11 cases of dysphagia lusoria. He claims that "detailed explanation of the *x*-ray films to the patient proved to be an effective therapeutic gesture." There is no follow-up available on these patients.

Case Report

A married woman aged 54 was first seen on July 16, 1959. About 25 years previously she had noticed some dysphagia on swallowing pills, which had to be crushed, or on attempting to swallow large or hard pieces of food. Her dysphagia was constantly present, but it fluctuated in intensity. About 14 years ago she found it impossible to lie flat in bed and had become used to having six to eight pillows. When lying flat she felt as if something in the chest moved up into her throat and caused swelling of the neck. This swelling would rise as far as the ears, but no higher, and it produced an intense sensation of discomfort amounting almost to angor animi. At the same time she noticed hoarseness of her voice and what she described as attacks of "laryngitis," by which she meant total inability to phonate, not associated with pain. All these symptoms waxed and waned. She would have attacks lasting up to three months, and intervals of comparative freedom lasting from 18 months to two years. During an attack she insisted that her neck was actually swollen. Her eyesight was not affected; she did not suffer headaches, and her general health was quite unimpaired.

There was one other curious symptom which defied explanation. She insisted that since childhood she had been unable to tell left from right, and this caused her much embarrassment at school and while she was in the Women's Auxiliary Services. During parades the platoon might be given the order to turn left or right and would duly go off in that direction, but she would invariably go off in the opposite direction. The only way she could find her bearings was by feeling her fingers and working out which was her left hand and which her right. In October, 1953, after the loss of a child, her symptoms became more noticeable, and she consulted a physician. An "*x*-ray of the oesophagus" was done, and this was reported to have been normal. After several visits to her doctor she was referred to a psychiatrist for treatment of the "globus hystericus." The psychiatrist made a note on his card that, in his opinion, this patient, although outwardly stoical, was a hysteric. He explained to her that she had a "wall of tears" in the chest, and that psychiatric treatment would enable her to have a good cry and rid herself of this wall. She refused treatment, and went back to her work as a doctor's receptionist. She had learnt to live with her symptoms previously, and, in the absence of medical help, would continue to do so.

She consulted me at a time when her symptoms were particularly bad. She said that she had been moderately well until a few days previously, when she had developed a cold, associated with tightness in the chest, "as if something was stuck." She had a feeling of wanting to belch, but the gas would only come up as high as the angle of Louis, and then would be propelled down and up the oesophagus, crackling and rumbling all the while. This symptom had persisted day and night for three days. She had been forced to sleep sitting straight up, because of a choking feeling on attempting to lie down, and she had avoided taking solids completely, as they appeared to stick in the region of the upper sternum. The swallowing of fluids, especially tea, gave some relief. Her voice had become more hoarse than usual, and the whole of her neck was swollen and tight. The attack, above her usual background of symptoms, had begun suddenly, accompanied at first by some nausea which soon passed off. Apart from the removal of her gall-bladder and appendix, she had always been in good health, and there were no other symptoms.

Examination

The patient weighed 128 lb. (58 kg.), and measured 5 ft. 4 in. (162.5 cm.). There was nothing peculiar about her habitus, and she looked younger than her 54 years. She sat upright in comfort, but became extremely dyspnoeic when reclining. The base of the neck looked full and tense, and the anterior jugular veins stood out like distended cords. The fullness of the neck suggested bilateral diffuse thyroid enlargement, which was in fact present, and over the region of the thyroid gland the neck was flushed. Her bearing was that of someone being gently choked by external physical means. In fact, she described the feeling in her neck as one of being so choked. The external jugular veins were not seen to be distended. There was diffuse tenderness around the base of the neck anteriorly. Blood-pressure readings were 110/70 (right) and 120/80 (left). The rest of the physical examination was unremarkable, except for the appearance of the optic fundi. Here the veins were over full and the disk edges were blurred bilaterally. After treatment these abnormalities resolved completely. The E.C.G. was normal, and the urine contained neither albumin nor sugar. The clinical impression gained was that of a retrosternal goitre which has undergone a recent haemorrhage.

The radiological diagnosis was made by Dr. A. Berezowski. In the postero-anterior view the typical oblique radiological defect in the oesophagus was seen (Fig. 3), and there was also an indentation on its postero-lateral aspect, caused by the aberrant vessel (Fig. 4). Aortography confirmed the presence of an aberrant right subclavian artery with a slight dilatation at its origin, the remainder of the artery being of normal calibre (Fig. 6). The right and left common carotids and left subclavian artery were normal.

Oesophagoscopy was performed by Mr. A. I. Lichter. From 20 to 22 cm. from the upper incisor teeth an obliquely running indentation of the posterior oesophageal wall was apparent. The indentation ran from left to right in an

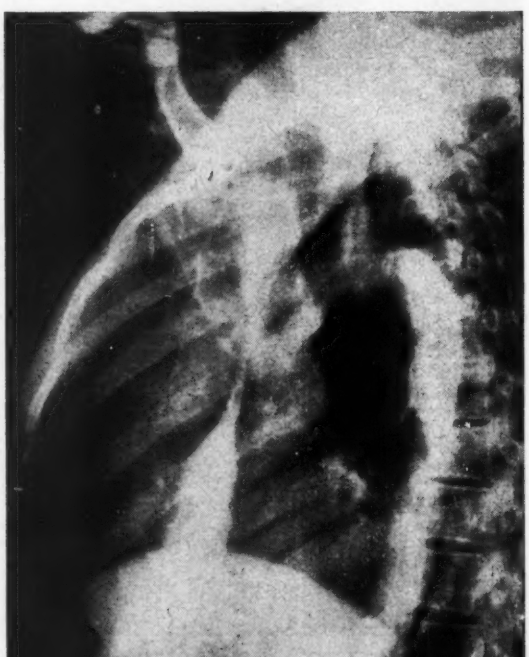

FIG. 6.—Angiogram, showing the aberrant right subclavian artery arising from the aorta, with slight dilatation at its origin.

upward direction corresponding to the appearances on the barium swallow. This area showed forceful pulsation. The remainder of the oesophagus showed no abnormality. While the oesophagoscope lay on and beyond the pulsatile swelling, the right radial pulse was completely obliterated. On withdrawing the oesophagoscope to just above the swelling, the pulse returned immediately. The left radial pulse remained constant throughout. These observations on the pulse were made by Mr. M. Arnold.

Operation (Mr. A. I. Lichter)

The left chest was entered through the bed of the resected fourth rib. The mediastinal pleura was incised and displayed the posterior mediastinal structures. The left subclavian artery and the aberrant right subclavian artery were identified. The aberrant artery arose about 0.5 cm. beyond the left subclavian from the posterior aspect of the aortic arch. The origin of the aberrant artery showed a slight aneurysmal dilatation. The artery was traced backwards and obliquely upwards towards the right. It was freed from its bed, where it lay between the posterior wall of the oesophagus and the spine. The thoracic duct was identified and retracted. The artery was freed up to the right border of the oesophagus and ligated at that level and at its origin from the arch of the aorta. The intervening portion of the artery was excised and on examination was found to show slight atheromatous changes. No fibrous bands accompanied the artery. In its final position the distal stump of the artery lay along the right border of the oesophagus. The chest was closed in layers with an underwater tube drain. The patient made a rapid recovery from the operation, with the immediate disappearance of all symptoms.

Results

At a follow-up examination on February 24, 1960, the patient insisted that immediately after coming round from the anaesthetic she was aware that all symptoms of the past 20 years had vanished. She was now able to lie flat, and, in fact, slept with no pillows. The hoarseness of the voice had disappeared. The optic fundi presented normal appearances, and there was no thyroid swelling. She was able to swallow anything and everything with ease. The size of her neck had returned to what it was 25 years ago.

Discussion

An aberrant right subclavian artery is fairly rare, but dysphagia lusoria is extremely so. It is possible that, with increasing recognition of the clinical syndrome, the two conditions will approach each other in incidence. It has been suggested that when symptoms are present they are due to the diverticulum of Kommerell; but this is unlikely, because symptoms may be episodic and also because, as the present case demonstrates, a relatively slight dilatation at the origin of the artery is compatible with symptoms severe enough to warrant a thoracotomy. Moreover, that part of the artery which causes the oesophageal obstruction is usually not dilated.

It is unlikely that increasing atherosclerosis or tortuosity of the vessel is important in symptom production, as will be seen from the age of onset in Palmer's (1955) 11 cases: three patients were 20–29 years, two 30–39, three 40–49, one was 50–59, one 60–69, and one 70+.

In symptom production we have to answer three questions.

1. Why, in the majority of cases, are there no symptoms at all? Possibly in most people the capacity of the superior mediastinum is such that the anomaly is accommodated freely.

2. Why, in some cases, are symptoms chronic and progressive, as in Bayford's original patient? Probably a combination of factors, local and general, associated with advancing age play a part—such as progressive aneurysmal dilatation of the vessel, emphysema, and kyphoscoliosis. All these would decrease the capacity of the already tightly packed mediastinum.

3. Why, as in the case described above, is this abnormality capable of producing a picture of superior mediastinal obstruction? It is clear from the clinical picture described that there was obstruction to the venous return from the head and neck, as evidenced by the swollen appearance of the neck, the flush, the enlarged thyroid, the appearance of the optic fundi, and the choking sensation. Anatomically it is unlikely that the innominate veins or superior vena cava would be compressed directly by the arteria lusoria, as they lie far forward in the mediastinum in front of the trachea. They could, however, be compressed, owing to their relatively low internal pressure, by oedema, although why any swelling should occur is not clear. Such oedema would be unlikely to affect the arteries with high internal pressures, or the trachea with its more rigid structure. The peristaltic waves of the oesophagus might, with difficulty, produce sufficient mechanical force to propel food through the area of relative obstruction—hence the lack of total obstruction and regurgitation.

So far as can be ascertained from the English-language literature, this is the first reported case of dysphagia lusoria presenting as a superior mediastinal syndrome. It is also the first time that an adult patient has been operated upon for the relief of symptoms due to an aberrant right subclavian artery.

Summary

Adult dysphagia lusoria is due to an aberrant right subclavian artery compressing the oesophagus. This disorder is probably not as rare as the paucity of case reports would suggest; methods are therefore described by which more cases of "globus hystericus" might be found to have an organic basis.

A case is described presenting as chronic superior mediastinal compression: complete disappearance of the symptoms and signs occurred after surgical resection. This is the first known adult patient to be operated upon for the condition.

My thanks are due to Dr. A. Berezowski for the *x*-ray films; to Mr. A. I. Lichter for his operation notes; and to Mr. A. M. Shevitz, of the Witwatersrand University Medical School, for the photographs.

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The sixth portion of the Signet Library, Edinburgh, consisting of seventeenth, eighteenth, and nineteenth century pamphlets and a few books, was sold recently at Sotheby's. A first edition, 1811, of Sir Charles Bell's *Idea of a New Anatomy of the Brain* went for £410.

GIANT-CELL ARTERITIS, OR ARTERITIS OF THE AGED

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Giant-cell arteritis, once believed to run a benign course, kills or maims a number of those afflicted, and when in remission it may only sleep. We hope for wider recognition of this common disorder, which is treatable for the most part, but if untreated may progress slowly with pain, palsy, blindness, deafness, and madness in its train, or sometimes more rapidly to a fatal termination. Diagnostic failure is due to many diverse presentations, some of which are little known, and to continued acceptance of a too rigid profile of the disease, despite the fact that the literature is replete with clinical and pathological evidence of its systemic nature. It must be emphasized that classical involvement of the temporal arteries may appear late, transiently, or possibly not at all during the period of observation; it is only one incident of a disorder phased in time and widespread in its distribution.

Hutchinson (1890) and Horton *et al.* (1932) must each be credited for giving temporal arteritis its entity. Gilmour (1941) extended the concept of the disease by pointing out that other arteries were often involved —namely, aorta, internal and external carotids, iliacs, coronary, occipital, and retinal arteries. Cooke *et al.* (1946) drew attention to "a widespread arterial disease, not uncommon, but rarely recognized," and brought the total number of case reports at that time to 37; their own cases, and others already published, illustrating well the poorer prognosis of the disorder. For economy of space, and as the object of the present article is a clinical study of 76 patients, the reader is referred for pathology to papers by Gilmour (1941), Cooke *et al.* (1946), Cardell and Hanley (1951), Heptinstall *et al.* (1954), and in particular those by McCormick and Neubuerger (1958) and Crompton (1959), which illustrate the impact of the disease on the smaller intracranial and meningeal vessels.

The precise relationship, if any, of this generalized arteritis of the aged to thrombo-angiitis obliterans, polyarteritis nodosa, "pulseless disease," and other "arteritic" states has yet to be determined. It is probable, however, that some patients with "aortic arch syndrome" (Gilmour, 1941; Bruce, 1950; McMillan, 1950; Ross and McKusick, 1953; Barker and Edwards, 1955; Harrison and Harrison, 1955) may be suffering from arteritis. It is also probable that thrombosis of the internal carotid artery in some patients arises from the same cause (Meneely and Bigelow, 1953). Extensive atheroma may coexist with arteritis, and, although the precise relationship of each to the other is yet unknown, nevertheless the effect is that atheroma frequently obscures the diagnosis, and so may hyperpiesis. A further complication in diagnosis, but of possible aetiological significance, is the fact that most of our patients gave a history of migraine or vascular headaches since their youth.

Bagratuni (1953, 1956) described the disorder he termed "anarthritic rheumatoid disease"; at that time one of us (Paulley, 1956) expressed the opinion that this condition was none other than temporal arteritis in one of its several guises. Clinical material collected since has supported this view.

Modes of Presentation

1. *Classical "temporal arteritis"* presents with severe head pains rather than headaches, and tenderness over the course of the temporal and occipital arteries, which may be reddened, thickened, and non-pulsatile. The patient is often febrile, with failing vision or blindness of recent origin in one or both eyes. Diplopia, ptosis, and oedema of the face and orbit occasionally occur. The fundi may show papillitis, avascular segments in the retinal arteries, perivasculitis giving the appearance of "sheathing" of the vessels, and exudates. Optic atrophy commonly follows thrombosis of the central retinal artery of its branches, or of the ophthalmic artery. Thrombosis of the retinal veins may also occur (Lander and Bonnin, 1956; Crompton, 1959; Ross Russell, 1959). "Anarthritic" rheumatism especially (see No. 7) and polyarthritis are frequent precursors, by months or years, and may not be mentioned unless specifically asked about. A raised E.S.R. is nearly always present, but by the Wintrobe method it was normal in five of our patients; the Westergren reading in one of these was 85 mm., and she was not anaemic. This is the method we now use. Electrophoresis often demonstrates increases in globulin fractions, especially alpha 2 and beta. Hypochromic anaemia and leucocytosis are frequent. Blood W.R. should be ascertained in all patients, and C.S.F. W.R. wherever possible in those with mental or neurological symptoms. Arterial biopsy is unnecessary in the classical disease, the diagnosis being self-evident, and if the presence of giant cells is made an absolute criterion of diagnosis it may even be misleading; intimal thickening, cellular infiltration, and thrombus formation being more constant findings.

2. *Head pains and headache and tenderness without classical stigmata.*

3. *Facial Neuralgia.*—Cases will be missed if red, pulseless, temporal arteries are insisted upon in diagnosis. More important is a history of severe pains in the neck, occiput, jaw, face, and head, of a type not previously experienced, with extreme tenderness, so that even the pressure of the head on a pillow is unbearable. The temporal and occipital arteries may not be involved at this stage, and we have seen instances where the disease has already dealt its blow to the temporals, leaving them recanalized, or painless fibrous strands. A negative temporal-artery biopsy, therefore, does not exclude the disease, because the vascular changes are patchy and subject to phases of activity (this is well illustrated by Cases 6, 12, and 15). Examination of the internal carotid and facial arteries should always be carried out; some patients show fusiform aneurysmal changes at the bifurcation (Pearse and Hinshaw, 1956) (see also Case 7), where thrombosis may supervene. Facial artery biopsy is sometimes more useful than biopsy of a temporal artery (see Cases 1–5).

4. *Madness (confusion, depression, dementia).*—Minor degrees of this disease are common in its classical form, but it is not sufficiently realized that severe mental changes may predominate, and be the only apparent

symptom. Many such patients must go undiagnosed to mental hospitals because this potentiality of the disease is not widely known. We have been able to find only one reference in the psychiatric literature (Vereker, 1952), though that author refers to several other articles in which mental symptoms were prominent. The reports by McCormick and Neubuerger (1958) and Crompton (1959) explain very clearly why mental symptoms are common by showing the widespread involvement of the intracranial and meningeal vessels. (See Cases 2, 6, and 7.)

5. *Visual.*—Blurred vision, partial loss of a visual field, transient blindness, or blindness should arouse suspicion of arteritis, and may be so obtrusive as to cause the patient to suppress other symptoms. Birkhead and Wagener (1957) record that 22% of 250 cases in the literature were rendered blind in both eyes, and they point to the 50–75% reduction in the incidence of blind eyes in steroid-treated patients. This presentation is well recorded in the ophthalmological literature, and constitutes one of the disease's worst hazards. (See Cases 2, 4, and 14).

6. *Cardiac Ischaemia.*—If coronary artery disease occurs as a complication of temporal arteritis, as is well known (Gilmour, 1941 ; Cooke *et al.*, 1946 ; Cardell and Hanley, 1951 ; Frangenheim, 1951 ; Morrison and Abitbol, 1955), it is logical that it may sometimes present in this way, but this as yet is rarely considered. Suspicions that a cardiac infarction may be a presenting manifestation of arteritis of the aged (or for that matter disseminated lupus erythematosus or polyarteritis nodosa, which require exclusion) arise when fever persists beyond the usual 7 to 10 days for no detectable cause, and where the E.S.R. remains high for weeks, or months, after the episode of infarction, and if the electrophoresis pattern is abnormal. (See Cases 8 and 15 ; and Case 12, third admission.)

7. *"Anarthritic" Rheumatism.*—Pains and stiffness in muscles of shoulders, arms, back, and legs (Bagratuni, 1953, 1956 ; Paulley, 1956). We suggest that this syndrome is none other than arteritis, in which the classical stigmata of the disease have yet to develop, or have already occurred. (See Cases 12–14.)

8. *Pain in Ear, Vertigo, Deafness.*—There are case reports in the literature of vertigo and deafness (Cooke *et al.*, 1946 ; Kendall, 1953). In our series we have two examples of pain in the ear lasting a few days, with severe vertigo and sudden deafness as the presenting symptoms ; in one of these the other ear was similarly affected a few weeks later, leaving the patient stone deaf. She first came to our notice a year afterwards with episcleritis, malaise and low fever, vertigo, weight loss, and "muzzy"-headedness ; all symptoms except deafness responded to steroid treatment. The pain and suddenness of the aural symptoms suggest a vascular lesion affecting the auditory apparatus, possibly in the same way that the optic nerve is involved by arteritis of the ophthalmic artery (Lander and Bonnin, 1956 ; Crompton, 1959). (See Cases 4 and 10.)

9. *Strokes.*—A few patients presented with strokes. The literature on temporal arteritis records patients having died of strokes (Cardell and Hanley, 1951), but at the time such events were often thought to be unrelated. Though all our patients with cerebral thrombosis had other symptoms and signs of arteritis, these tended to be overshadowed by the major catastrophe, and to be overlooked unless sought for.

10. *Vomiting and Cachexia Suggesting Neoplastic Disease.*—On two occasions patients were referred as probable advanced cases of carcinoma. Both patients were wasted, and were vomiting most of their meals. Generalized limb and back pains suggested widespread skeletal metastases. Vomiting occurred twice in our series when steroid dosage fell too low. (See Cases 8 and 10.)

11. *Masquerading as Meningeal Irritation or Subarachnoid Haemorrhage* (Keen, 1950).—These patients present with severe pains and stiffness in the neck and occiput, but are without abnormal vessels on clinical examination. In spite of the fact that Kernig's sign is usually negative, they require lumbar puncture, and the C.S.F. protein may be raised, usually without an increase in cells. (See Cases 2 and 3.)

12. *Pyrexia of Unknown Origin.*—Another clinical presentation is fever of unknown origin, as seen, for example, on the second admission of Case 8 and as a predominant symptom at the time of admission in Cases 5, 6, and 9.

13. *Polyarthritis.*—Polyarthritis of the rheumatoid type, with frozen shoulder, also occurs, but is perhaps less common than the anarthritic type of rheumatism.

14. *Aortic Arch Syndrome.*—At the risk of being controversial we suggest that arteritis should be thought of as a possible cause in patients with occlusive disease of the aorta and its main branches, and in dissecting aneurysms of the aorta (McMillan, 1950) ; this is borne out by Cases 7 and 11, and by the articles referred to earlier.

Discussion

Series.—From 1953 to 1959 we recognized and treated 76 patients with arteritis of the aged (see Table). Their ages ranged from 54 to 88 at the onset. 75 were followed up ; 8 are dead. Many were missed in the earlier period of study because of failure to recognize atypical presentation.

Nomenclature.—We suggest the possible use of the term "arteritis of the aged" in an attempt to convey the systemic nature of the disease. There are some objections to "giant-cell arteritis" because giant cells are not always present in the smaller vessels. It must also be admitted, however, that not all sufferers are very old.

Psychosomatic Factors in Aetiology.—A depressive state, often concealed, invariably precedes the somatic manifestations of the disease by a few weeks or months and commonly arises from the death or marriage of a near or dear one. However, deaths of cats and dogs were provocative on two occasions in this series. Deprivation other than by death—as, for example, by admission of a beloved person to hospital, especially mental hospital—occurred in a number of our cases. Marriage of sons or daughters incurring separation, especially emigration, and ungracious treatment by relations of recently bereaved old people were recurrent features. The types of stress precipitant, and the personality make-up, are not at present distinguishable from those found by one of us (J. W. P.) in most collagen diseases, particularly rheumatoid arthritis.

Anarthritic Rheumatism.—No proof is advanced that all cases hitherto described are identical with arteritis of the aged, but the circumstantial evidence is in favour. Anarthritic rheumatism as Bagratuni described it, and

the prodromal rheumatism as seen in our patients, appear to be the same. In arteritis of the aged the rheumatic phase may be prolonged, and usually precedes other symptoms by weeks, months, or years, but it may succeed them. There are occasional examples of dramatic shift of symptoms, from incapacitating rheumatism to cranial manifestations overnight, as in Case 14 and another of our patients.

Diagnosis

In a recent series reported by Ross Russell (1959) diagnosis was made in most cases on clinical grounds; biopsy was done in 11 out of 35 cases. In the present series it was done in 23 out of 76 cases. With increasing experience it now seems an unjustifiable procedure in the very elderly, who are so often unwilling to enter hospital. The small segment of artery available to the histologist, the patchy nature of the disease, its phases of activity, the fact that ophthalmic, intracranial, and meningeal vessels may be more heavily involved than vessels easy of access (McCormick and Neubuerger, 1958; Crompton, 1959) at once place a limited value on temporal-artery biopsy as an absolute criterion of diagnosis. Facial-artery biopsy has sometimes been helpful, and we tentatively suggest that biopsy of the spinal meninges in those patients with stiff backs and necks might be rewarding as a research method if the opportunity ever offered. Random scalp biopsy and muscle biopsy have been unhelpful in atypical and anarthritic rheumatoid patients in this series.

In cases presenting with predominant involvement of the aorta, coronary, carotid, intracerebral, meningeal, ophthalmic vessels, and those of the auditory apparatus, biopsy proof is obviously impossible during life. It is our contention that a clinical diagnosis is justified if one appreciates the natural history of the disease, the recorded necropsy reports (see references), the symptoms, signs—especially in the eye—and the laboratory findings in the form of a high E.S.R. and abnormal protein electrophoresis. On this basis a trial of treatment during life without positive biopsy is preferable to the risk of madness, blindness, or death.

Treatment

Other studies have shown how essential treatment with steroids is in this disease (Whitfield *et al.*, 1953; Harrison and Harrison, 1955; Birkhead and Wagener, 1957; Ross Russell, 1959). Occasionally large doses of prednisone, such as 30 mg. t.d.s., are needed to control the acute stage of the disorder; usually 10 mg. b.d. is effective, but twice in this series A.C.T.H. has controlled the disease where prednisone was only partially successful.

As in rheumatic fever, rapid "tailing" is dangerous and relapse is frequent. A few patients have been successfully "tailed off" steroids after 6 to 12 months and have not relapsed over a period of observation of two to three years, and it may be that several of our more recent cases will eventually join this group. We have sufficient evidence, however, to show that maintenance on steroids indefinitely is beneficial for some patients.

It seems wise to try to discontinue steroid therapy after 6 to 12 months (with a preference for the longer period) and subsequently to observe the patient for signs of clinical relapse, raised E.S.R., anaemia, or fever.

If some emphasis has been laid on psychosomatic factors it is because their evaluation, though admittedly

Details of Series; 76 Patients (36 Male, 40 Female)

Age 80+	70–79	60–69	50–59	Widows	Widowers	Single	Stress Related to Onset	Presenting with Eye Symptoms
12	30	29	5	20	12	8	70 (70)	30

Referred from Eye Dept.	Obliterative Arterial Disease of Eye	Obliterative Disease of Veins of Eye	Presenting with Classical Temporal Arteritis	Presenting Atypically with Head Pains and/or Facial Pains but without Abnormal Vessels to Feel
13	28	2	32	31

Mental Symptoms Prominent	Mental Symptoms Predominant	Presenting with Cardiac Infarction or Angina Pectoris	Presenting with Cerebral Thrombosis	Meningeal Irritation	Dissecting Aneurysm of Aorta
35	12	9	8	3	2

Anarthritic Rheumatism	P.U.O. Presenting Problem in Diagnosis	No. Followed Up, 75		Mode of Death				
		Alive	Dead	Left Heart Failure	Cardiac Infarction	Cerebro-vascular Accidents	Dissection of Aorta	Uraemia
32	16	67	8	4	3	2	1	1

Effect of Treatment with Steroids (No. Treated, 73)				3 Untreated Patients (Female)		
Excellent 51	Good 12	Moderate 6	Poor 3	Temporal artery biopsy 1954. Remitted. Remains well	Diagnosed 1956. Chronic ill health. Anaemia, head pains, vertigo, rheumatism. On and off since	Classical temporal arteritis 1959. Remitted spontaneously. Remains well under observation

Relapses on Reduction or Cessation of Steroids	Clinical Features and Investigations						
	Fever 100° or More	Anaemia Less than Hb 80%	Raised E.S.R. (Wintrobe)	Abnormal Protein Electrophoresis	Artery Biopsy Done	Positive	Giant Cells Present
29	30	23 (62)	67 (72)	28 (34)	23	21 (23)	10 (23)

Totals do not tally because of multiple presentations, and multiple admissions in a few patients with different presentations, as in Mrs. F and Mr. L. Figures in parentheses indicate the number of patients involved where this is less than the whole series of 76.

controversial in aetiology, has been found of considerable importance in treatment. In our experience, relapse is unlikely where the provocative emotional stress is non-recurrent; but where these old people have to live in an unrelieved stressful situation, or have been unable to accommodate, doctors need to be vigilant, and steroids may have to be maintained for a long time. What the level of maintenance should be is a matter for individual determination; prednisone, 5 mg. once or twice daily, appears to be too low initially. Most cases remain well on 12.5, 15, or 20 mg. of prednisone a day. Skeletal osteoporosis has to be looked for during long-term treatment and countered by suitable oestrogen and androgen preparations and calciferol. To date we have not had complications from intercurrent infection. Vomiting or refusal to take steroids should be immediately reported; this constitutes an emergency about which patients, their relatives, and doctors should be warned.

Because of the smouldering nature of the disease, and the severity of its complications, we advise the closest supervision of patients in apparent remission.

We give below the history of 15 cases; the Table on p. 1564 correlates details of the series.

Case-histories

Case 1.—In October, 1959, Mrs. A, aged 62, presented with malaise, nausea, excruciating pains in right face, temple, and occiput for five weeks; temperature 99–100° F. (37.2–37.8° C.); she became aware of tender spots on scalp, but none were visible or palpable. Facial, occipital, and temporal arteries normal. E.S.R. 35 mm./hour. Electrophoresis, α_2-globulin increased. Hospital admission not sought; the diagnosis being evident, she was treated with prednisone, with an immediate response. A month later, a mild relapse on dose being reduced to 5 mg. b.d.; she remained well on 5 mg. t.d.s.

Case 2.—Miss B, aged 63. Nervous breakdown in 1956 after domestic discord. Central retinal venous thrombosis occurred shortly afterwards—a recognized eye manifestation of arteritis. Admitted September 8, 1959, for suspected meningitis or subarachnoid haemorrhage with a three-weeks history of neck stiffness, occipital pain; finally, fever 100° F. (37.8° C.) for two days, drowsiness, dysarthria, and mental confusion. Examination revealed no abnormal vessels. C.S.F. and blood W.R. negative. E.S.R. 48 mm. Hb 89%. No L.E. cells. Plasma protein globulin 4 g.%, increase in α_2. Immediate response to predisone 10 mg. t.d.s. in 12 hours. She stated the morning after admission: "It's floated away; it's just like heaven." Dysarthria and full mental faculties took about a week to recover.

Case 3.—Mr. C, aged 80, was depressed after his wife's long illness and death. He had occasional headaches; with increasing unhappiness in his environment, however, in November, 1957, he suddenly developed severe temporal and occipital headache, and was unable to bear pressure of head on pillow. Mental confusion began to occur at night. Superficial scalp vessels normal to feel, occipital tenderness was present. B.P. 180/100. E.S.R. 9 mm./hour Wintrobe. W.R. negative. Being unwilling to enter hospital he was treated with prednisone and lost his symptoms in 24 hours. Three months later he stopped taking prednisone against advice, fearing addiction. Headaches recurred. Subsequently prednisone was taken only when he had headaches, as if it were aspirin. Mental confusion did not recur, but he died elsewhere of cardiac infarction in September, 1958, after several lesser heart attacks.

Case 4.—Mr. D, aged 67, had lost his wife and took to drink; he was seen in September, 1958. Had had sudden pain in right side of head and ear a year before, followed by giddiness and deafness on that side. Memory deteriorated and he was unable to concentrate or do his job properly. Deafness persisted. During summer of 1958 he had transient attacks of blindness in left eye; ophthalmological opinion was that temporal arteritis should be considered, the fundus being avascular and the vessels showing considerable irregularity. B.P. 170/90. E.S.R. 32 mm./hour. Hb 86%. W.B.C. 5,000. W.R. negative. Prednisone 5 mg. q.i.d, with immediate improvement mentally, and he was able to work normally. No further attacks of transient visual losses, but some deterioration of memory and concentration on dose of 5 mg. b.d. Symptoms again remitted on 5 mg. q.i.d. (October, 1959).

Case 5.—Mrs. E, aged 70, a depressive, jealous widow, with a domestic situation full of strife, was referred in April, 1958, for P.U.O. and malaise. Direct questioning produced a story of intense pains in head, neck, and jaws, beginning four months previously; had had to hold her head in her hands all night. When seen she had had no pain for three weeks. Night temperature 100° F. (37.8° C.). Hb 54%. E.S.R. 45 mm. Wintrobe (corrected). Cranial vessels appeared normal, but pigmentation was observed over the course of temporal arteries. She told of a sensation like "egg-shell crackling" when she had touched her temples some weeks before. There was immediate response to prednisone, and she remained well on a maintenance dose of 5 mg. b.d.

Case 6.—Mrs. F, aged 68; admitted April 26, 1955, with three weeks' history of pains of great severity in neck, jaws, and both sides of face, backache, vomiting, poor memory, confusion, and disorientation. She had had vertigo four years previously. She was very worried by a "simple" sister who had lived with her three months and needed constant supervision. A psychiatrist advised immediate admission to mental hospital with diagnosis of "paraphrenia with delusions and hallucinations." When seen by one of us on the same day, she was wild-eyed and in great pain, sitting up with her face in her hands. She was able to point to the tender areas over the facial, temporal, and occipital arteries, which were grossly thickened. Biopsy positive. W.R. negative. Hb 73%. E.S.R. 38 mm. Immediate return to "sanity" on cortisone 25 mg. q.i.d. in 24 hours, and relief of pain. After six months' maintenance on cortisone 50 mg. b.d. she was "tailed off" gradually. On February 6, 1956, she was readmitted as an emergency, complaints then being lassitude, insomnia, slight occipital headache, and three weeks' fever at nights. 99–100° F. (37.2–37.8° C.). On examination the most notable feature was mental apathy; there were no abnormal superficial vessels. E.S.R. 36 mm. Hb 58%. W.B.C. 9,300 (polys 84%). B.P. 110/70. Immediate response of all symptoms and fever on reintroduction of cortisone. Her own doctor then kept her on a maintenance dose of cortisone, but by November, 1959, she was having only 12.5 mg. a day. In October, 1959, her daughter was admitted to a mental hospital to patient's great distress. Three weeks later she followed her daughter to the mental hospital with precisely the same clinical presentation as in 1955, but no abnormal vessels were to be found. Prednisone 20 mg. t.d.s. was needed to bring this episode under control in a week.

Case 7.—Mrs. G, aged 72, attended on October 21, 1959. For six weeks she had had stiffness and soreness of shoulders, hips, knees, and ankles, with swelling of the latter. For weeks previously she had pains in the neck and, at the outset, sweats. Mild frontal and occipital headaches had been present for six years. She had been "losing herself" since onset, imagining things that had not happened and having no memory for recent events. For two weeks she had been somnolent. Examination revealed so slight a degree of redness and thickening of the left temporal artery as to have normally escaped attention. Biopsy positive. There was aneurysmal dilatation of bifurcation of left common carotid, aneurysmal dilatation of aortic arch with inner ring of calcium, aortic incompetence; B.P. 200/115. Fundi—no papilloedema, arterial irregularity, and exudate and a haemorrhage (right). Hb 65%. W.B.C. 8,200 (polys 83%). E.S.R. 33 mm. Electrophoresis: globulin 3.4 g.%; increase in α_2-globulin. L.E. cells negative. C.S.F. normal.

W.R. negative The patient was febrile, 100° F. (37.8° C.), and very confused. Prednisone, 20 mg. q.i.d. for a few days, and then reduced, produced dramatic recovery, enabling her to return home on November 10 on prednisone 10 mg. b.d. Her husband's last report is that "she is sensible and doing her housework; her relatives are amazed." The family thought her depression was due to the admission of a favourite niece to a mental hospital a few weeks before onset.

Case 8.—Mr. H, aged 86, admitted on November 12, 1956. Referred for suspected carcinomatosis. In 1954 he lost his wife unexpectedly from pulmonary embolism and became depressed. In April, 1956, he consulted his doctor because of dyspnoea and palpitations. Auricular fibrillation was present. Subsequent E.C.G. suggested that he had had a silent cardiac infarction. He said he had felt tired ever since his wife's death, and for several months had had pains up his back, pain and weakness in legs making walking difficult, nausea, anorexia, loss of weight, stiffness in the mornings "all over," and "pain in jaw on chewing." Examination revealed a thrombosed right facial artery. Biopsy positive. E.S.R. 27 mm. B.P. 180/80. W.B.C. 8,000 (polys 78%). Immediate and dramatic response to cortisone 25 mg. q.i.d. Maintained since on 25 mg. b.d. He remains well.

Case 9.—Mr. I, aged 68, admitted on March 23, 1956, for P.U.O. Night temperature 101° F. (38.3° C.); depression for three months. A history of sharp head pains at the outset had to be dragged out of him. Hb 56%. E.S.R. 30 mm. Temporal artery biopsy positive. Immediate response to cortisone. Remains well; off steroids two years.

Case 10.—Mr. J, aged 75; admitted on November 6, 1956. Referred with diagnosis of carcinomatosis and heart failure. Vomiting and loss of weight were presenting features of a few weeks' duration, and swelling of legs for two months. Five months previously he had had severe pains in left leg and in his shoulders, then spreading all over him, including his head. He also complained of a "frog" in his ears, and tinnitus, smarting eyes, and dizzy spells. His gait had been unsteady. He lived alone since his wife's death in 1949, but had become very depressed after recent death of a son-in-law. Temporal arteries were red, thickened, non-pulsatile, and visible from the door; biopsy was done, but was technically unsatisfactory. E.S.R. 32 mm. Hb 74%. W.B.C. 5,200 (polys 78%). C.S.F., increase in globulin. W.R. negative. Cortisone 25 mg. q.i.d. brought relief of all symptoms. Maintenance on 25 mg. b.d. was stopped in November, 1957. He has remained in excellent health since without steroids.

Case 11.—Mrs. K, a widow aged 70, had had headaches all her life. In August, 1957, intensity of head pains increased in left temple, with blurring of vision a month later. In October she had bilateral papilloedema, and the left temporal artery was nodular and non-pulsatile. A diagnosis was made elsewhere of arteritis of temporal and retinal arteries by an eminent physician. Biopsy was refused. E.S.R. 49 mm. Urine: R.B.C., polys, urea 37 mg./100 ml. W.B.C. 10,000 (polys 71%). B.P. 230/120. W.R. negative. A few months later she developed a large dissecting aneurysm of the arch and descending aorta. She died in her sleep in September, 1958. Prednisone relieved her headache, but she developed increasing signs of heart failure after her aortic catastrophe.

Case 12.—Mr. I, aged 69, was admitted on February 1, 1954, with pain and stiffness in shoulders, back, thigh, calves, and right wrist for six weeks. Retired manager (three years); wife died 16 months previously. He had had a shock when a sister with whom he was staying died suddenly at Easter, 1953. Depressed by unhappy relationship with daughter. He was febrile 99.2° F. (37.3° C.). E.S.R. 30 mm. Hb 78%. B.P. 180/85. Rheumatoid arthritis was diagnosed. He responded immediately to cortisone and mobilization; the drug was tailed off over two weeks, being followed by a short course of A.C.T.H. and physiotherapy as out-patient. By April 16 he had relapsed. Readmitted on May 27 with temporal headaches, and had seen an eye specialist because of sudden pain in left head and deteriorating vision in left eye. The left disk showed a papillitis and some exudate. V.A. 6/36. Left temporal artery tender, thickened, but pulsating. Diagnosis, temporal arteritis. Treated with cortisone for three weeks and then A.C.T.H. for seven days, with recovery. On February 20, 1956, emergency admission with cardiac infarction after three months' lethargy, and angina of effort. Died.

Case 13.—Mrs. M, aged 68, a depressive, martyred widow, distressed over recent emigration of her son and marriage of her daughter to a foreigner, attended as out-patient on November 16, 1959, with a history of aching legs for two years. Her back became affected in August, 1959: "like being in a plaster cast." When seen she had pains in shoulders, back of legs, and for one week violent pains up the back of her neck—"to drive me crazy"; unable to move unassisted. No temporal or jaw pain, but "muzzy-headed" at times. Tender over upper dorsal spines, nowhere else. Stiff neck and shoulders and back. B.P. 160/80. Febrile 100° F. (37.8° C.). Hb 84%. W.B.C. 13,400. E.S.R. 40 mm. Electrophoresis: globulin 4.4 g.%; increase in α_2 and β fractions. L.E. cells negative. Blood culture sterile. Skeleton normal. Immediate complete response to prednisone; now on maintenance 5 mg. t.d.s.

Case 14.—Mrs. N, aged 70, was seen on January 7, 1959. Fifteen months previously, after retirement from work, and the death of her cat by poisoning, she became depressed. Rheumatic pains in knees, back, and shoulders quickly followed. She was severely disabled. One morning in November, 1958, she woke to find all her rheumatism gone, instead she had pains in her head and jaw. Three weeks later she had diplopia and then blindness in her left eye. She had tinnitus and had been stumbling and veering to the right for five months; was anaemic, had lost weight, and was losing vision in her remaining eye. Clinically, she had classical temporal arteritis, with bilateral papillitis and absent left light reflex; the left eye was quite blind. Hb 75%. E.S.R. 26 mm. W.B.C. 6,600 (polys 68%). Normal plasma globulin. There was a good response to prednisone 10 mg. t.d.s., and the right eye recovered. She remained well on prednisone 5 mg. b.d. She presents an example of the way this disease appears to switch its point of attack—sometimes, as here, literally overnight.

Case 15.—Mr. O, aged 65; admitted on May 5, 1959, with sudden ischaemic chest pain. E.C.G. confirmed anterior cardiac infarction. S.G.O. transaminase 90 units. After three weeks of persistently raised temperature, and with E.S.R. 34 mm., basal crepitations, electrophoresis globulin 4.4 g.%, with all fractions increased; polyarteritis nodosa suspected, but skin and muscle biopsy and L.E. cells negative. Immediate response of signs and symptoms to prednisone 5 mg. t.d.s. Discharged on maintenance dose of steroids, but these were stopped for some reason after five weeks. Within a fortnight he was admitted to another hospital with classical temporal arteritis. The clinicians there were surprised by a negative biopsy, but their faith in the diagnosis remained unshaken.

Summary

Seventy-six patients with arteritis of the aged (giant-cell arteritis) have been seen since 1953, approximately half of them in the last 12 months.

Case-histories have been selected to illustrate the lesser known presentations of a common disease which we believe must often confront psychiatrists, rheumatologists, neurologists, cardiologists, vascular, E.N.T., orthopaedic surgeons, and geriatricians, not to mention ophthalmologists, who are perhaps most aware of it, and general practitioners and physicians.

When elderly people begin to fail mentally or physically this should be one of the first disorders to be considered, and not one of the last.

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MODE OF ACTION AND SIDE-EFFECTS OF PHENFORMIN HYDROCHLORIDE

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The hypoglycaemic action of phenformin hydrochloride (phenethylbiguanide; "dibotin"; D.B.I.) has been observed in all types of diabetes. It has been the cause of some concern that its use can be associated with the appearance of ketonuria and acidosis in the presence of normal or slightly elevated blood-sugar levels (Hall *et al.*, 1958; Steiner and Williams, 1959). This occurs chiefly in the juvenile diabetic (Walker and Linton, 1959a). It is uncertain whether this anomaly is specifically caused by D.B.I. or whether it is due to absolute or relative lack of insulin. The object of this paper is to report some clinical features of the acidosis and to relate them to the present hypotheses of action of D.B.I.

Clinical Observations

Observations were made on a series of 109 diabetics of all types controlled on D.B.I. either alone or with supplementary insulin. Good control was often obtained, as judged by the accepted criteria. The results of part of the series are reported elsewhere (Walker and Linton, 1959b). Interest was drawn to the occurrence of ketonuria in the presence of normal or only slightly elevated blood-sugar levels. It was found that ketonuria was accompanied in 11 cases by frank reduction in alkali reserve.

It will be seen from Fig. 1 that a severe fall in alkali reserve was virtually confined to juvenile diabetics, although ketonuria appeared in all types. This seemed important and was thought to be related to the basic difference between adult and juvenile diabetes—that is, the presence or absence of endogenous insulin (Wrenshall and Best, 1956). It was then observed that there was an association between the appearance of acidosis and the amount of exercise taken. Close inquiry confirmed that any moderately severe physical exercise tended to produce ketonuria and acidosis in juvenile diabetics on D.B.I. It was further observed that the fresh urine from the patients on D.B.I. alone had a *p*H of less than 5.6, while the urine of other diabetics almost without exception exceeded this.

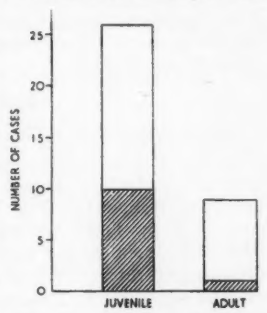

FIG. 1.—Incidence of ketonuria with or without acidosis in 102 cases. White columns = Ketonuria alone. Hatched columns = Ketonuria with acidosis. (Acidosis = alkali reserve below 20 mEq/l.) Note: "Juvenile" includes two juvenile-type adults with acidosis.

About this time the urgency of the problem was emphasized by the occurrence of two cases of very severe acidosis among the patients on D.B.I. (Walker and Linton, 1959a). Both were admitted to hospital in what appeared to be a diabetic coma. Case 1 had a blood-sugar level of 208 mg./100 ml. and an alkali reserve of 4.9 mEq/l. In Case 2 the respective values were 280 mg./100 ml. and 3.1 mEq/l.

The latter patient died despite strenuous empirical measures—intravenous glucose, insulin, and alkali—designed to combat acidosis. In neither case was there any obvious predisposing factor, and in both cases the biochemical upset was rapid in onset and severe in degree. Case 1 was controlled solely with 100 mg. of D.B.I. daily and is now controlled with 56 units of insulin. Case 2 was having 150 mg. of D.B.I. daily with 12 units of I.Z.S. ("lente" insulin).

A further case which threw some light on the problem was admitted some months later. There was severe acidosis and elevation of blood sugar; D.B.I. had been omitted for two days (blood sugar, 512 mg./100 ml.; alkali reserve, 15.2 mEq/l.) and again empirical methods were used. Insulin was given by intravenous and intramuscular routes, to a total of 280 units in the first 12 hours. In the first four hours, while blood sugars fell in the anticipated way, the alkali reserve deteriorated, reaching 5.8 mEq/l.; the alkali administered had been sodium lactate. Thereafter sodium bicarbonate was substituted, and the desired effect was obtained in a sharp rise of the alkali reserve.

Normally, intravenous administration of sodium lactate will result in an increase in the alkali reserve, as the lactate ion is either quickly metabolized in the Krebs cycle or converted to glycogen, leaving the sodium ion free to form sodium bicarbonate. In this case the further metabolism of lactate is probably blocked, and it contributed to the increased pool of lactate which is already present in patients on D.B.I.

Experimental Observations

It was decided to compare the response to exercise of patients on D.B.I. with that of normal and insulin-controlled patients, in terms of their blood sugar, alkali reserve, total blood hydrazones, and, in the latter part of the series, blood lactic acid levels.

A standard amount of exercise related to weight and age was given (Master and Oppenheimer, 1929). The exercise was not extreme and did not produce more than transitory changes in normal individuals. The specimens were taken before and after exercise and again 15 minutes later.

Results

Blood-sugar Levels.—There was no significant change.

Alkali Reserve.—The normal controls and the diabetics on insulin showed either no change in alkali reserve or a slight fall (Fig. 2). The groups of diabetics controlled by D.B.I. showed two types of response. With one exception, the unstable cases had a precipitous fall in alkali reserve after exercise, and 15 minutes later this fall was greater. The stable (adult) diabetics showed a fall in alkali reserve only slightly greater than that of the normal patients and diabetics not having D.B.I.

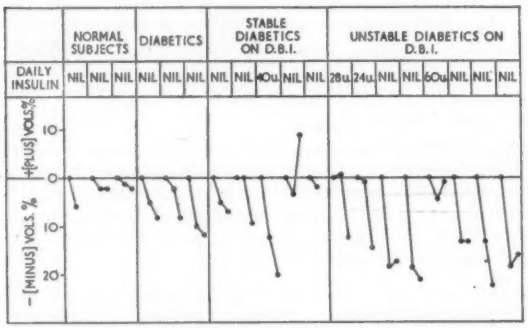

FIG. 2.—Change in alkali reserve in four groups of patients after standard exercise and 15 minutes later. Note the greater reduction of alkali reserve in unstable diabetics on D.B.I.

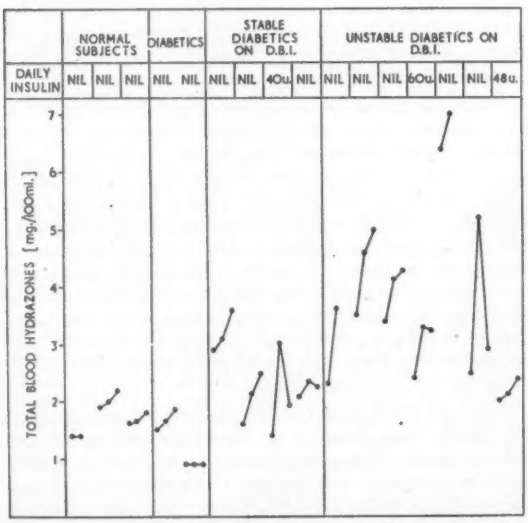

FIG. 3.—Total blood hydrazone levels before and after standard exercise and 15 minutes later. Note the higher initial levels and greater rise shown by unstable diabetics on D.B.I.

Total Blood Hydrazone (T.B.H.) Level.—This method was adopted as a simple, quick, and approximate means of detecting blood pyruvic acid. Friedemann and Haugen (1943) have measured pyruvic acid and T.B.H. before and after exercise and have shown that these are increased in proportion and the difference between them is small. Although a very approximate method, it was ideally suited to the investigation in hand. Fig. 3 shows that the levels were high in the unstable D.B.I. cases and climbed to higher levels after exercise. Again the stable D.B.I. cases were only slightly higher than the levels found in normal controls or insulin-controlled diabetics.

Blood Lactic Acid (Barker and Summerson, 1941).—As shown in Fig. 4, the change in blood lactic acid was

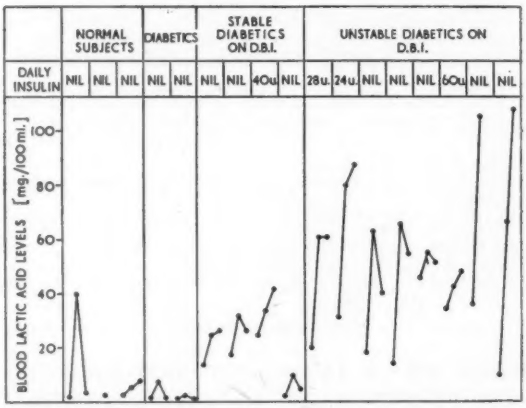

FIG. 4.—Blood lactic acid levels before and after exercise and 15 minutes later. Note the higher initial levels and greater rise shown by unstable diabetics on D.B.I.

the most striking one detected. The group of normals and diabetics on insulin showed a normal resting lactate level, a small rise after exercise, and a return to normal in the third specimen. The less stable diabetics on D.B.I. showed a high resting level, a large rise, and only a slight fall after 15 minutes. Stable diabetics treated with D.B.I. again differed little from normals.

Discussion

The hypoglycaemic effect of D.B.I. is independent of the presence of active β cells in the pancreas, in contrast to the arylsulphonylureas (Nielsen *et al.*, 1958). While glucose uptake is increased by D.B.I. *in vitro* (Odell *et al.*, 1958), the drug does not cause an increase in muscle or hepatic glycogen—in fact, the latter is reduced (Tyberghein and Williams, 1957; Williams *et al.*, 1957). The rise in blood pyruvate and lactate levels which occurs after the administration of D.B.I. is greater than that occurring with insulin (Klein, 1942; Fajans *et al.*, 1958). The hypoglycaemia and the increase in blood pyruvate and lactate are striking biochemical changes induced by the drug, and two hypotheses have been advanced to account for these phenomena.

The earlier hypothesis advanced by Steiner and Williams (1959) offers the explanation of defective utilization of lactate due to partial blockage of the tricarboxylic acid (T.C.A.) cycle. This they attribute to the demonstrable action of D.B.I. in poisoning certain necessary enzymes, particularly succinic dehydrogenase and cytochrome oxidase (Steiner and Williams, 1958). To maintain a store of high-energy phosphate bonds, an

increased emphasis is then placed on the normal glycolytic conversion of glucose to pyruvate, resulting in a lowering of blood-sugar level and increased production of pyruvate and lactate, which accumulate in the blood. A further factor which may contribute to the lowering of the blood-sugar level is decreased gluconeogenesis, for intermediates of the T.C.A. cycle are necessary for the conversion of some of the keto-acids derived from proteins to glucose. The net result of the process will be a depletion of liver glycogen, which in turn will favour the formation of ketone bodies from breakdown of fatty acid. Ungar (1959, unpublished observations), on the other hand, has suggested that there is increased production of pyruvate and lactate due to increased activity of the hexose monophosphate shunt.

The results here reported demonstrate that diabetics controlled by D.B.I. suffer from persistent biochemical abnormalities, despite apparently satisfactory control of the diabetes.

The abnormalities are of two types, which are not directly related, and either may occur in the absence of the other. The first anomaly to which attention was drawn was ketonuria with normoglycaemia. This occurred in diabetics of all types, and it is not yet possible to throw any light on the mechanism. It has been suggested that this represents a starvation ketosis; but all patients in whom it was observed were having at least 170 g. of carbohydrate daily, and with a few exceptions their blood-sugar levels were between 100 and 200 mg./100 ml. It would seem that the phenomenon may be the result of low stores of liver glycogen, secondary to lack of insulin. It may be that D.B.I. does not duplicate the antiketogenic effect of insulin, and a form of "metabolic starvation" occurs: adequate carbohydrate and protein are ingested and retained, but intermediate metabolism is disturbed by the lack of insulin, the effects of which are only partly replaced by D.B.I.

The second and more important biochemical abnormality found is that of acidosis of varying degree, occurring exclusively in juvenile-type diabetes and usually accompanying ketonuria. This seemed to be due, at least in part, to raised blood lactate and pyruvate levels, the latter being measured by T.B.H. levels—these having been found to be raised considerably in patients otherwise controlled on D.B.I.

The elevated basal levels of T.B.H. and blood lactate can be explained by either of the hypotheses of action of D.B.I. mentioned above. The very moderate exercise to which the patients were subjected is enough to provoke a large and sustained rise in blood lactate and T.B.H. and a large fall in alkali reserve. This suggests that intermediate carbohydrate metabolism is abnormal in diabetics on D.B.I. While it would appear to favour the hypothesis which suggests that lactic acid is more slowly disposed of owing to delay in the T.C.A. cycle, it is conceivable that the sudden call for energy leads to metabolism of glucose by any route, including abnormal paths which give increased production of lactate.

Thus D.B.I. is an effective agent for reducing blood-sugar levels in diabetic patients, but in the absence of insulin there may be disproportionate accumulation of intermediate products. It seems likely that, in the stable diabetic, endogenous insulin compensates for this to some extent. It must also be emphasized, however, that this effect can and does occur in the presence of substantial doses of insulin. This suggests that the biochemical disturbances may not be due simply to lack of insulin, but may in fact constitute a direct toxic effect of D.B.I.

Summary

Phenformin hydrochloride (D.B.I.) is an effective oral hypoglycaemic agent and compares well with the arylsulphonylureas.

Gastro-intestinal side-effects are commonly reported but are not dangerous. The appearance of ketonuria and acidosis has received little attention; it seems to be due to the drug's inability to duplicate all the actions of insulin.

Experiments are reported showing the effects of exercise on diabetics controlled by D.B.I. Unstable cases controlled by D.B.I. may show a marked fall in alkali reserve and a large rise in blood lactate and total blood hydrazones; the changes are much in excess of those observed in insulin-controlled diabetics and in stable cases on D.B.I.

It is emphasized that the acidosis may be dangerous, and the use of D.B.I. in juveniles cannot be recommended at this stage.

It is a pleasure to acknowledge the help and encouragement of Dr. A. C. Aitkenhead, in whose unit this work was carried out. The biochemistry department of Law Hospital has assisted with many of the estimations, and Sister Ferguson and the staff at the Strathclyde Diabetic Clinic have also been of great help.

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The Association of Universities of the British Commonwealth has recently published a booklet, *United Kingdom Postgraduate Awards 1960-62*, the purpose of which is to set out in a form suitable for quick reference summarized information about fellowships, scholarships, grants, etc., tenable at universities in the United Kingdom. The booklet also includes a short list of awards that can be held outside the United Kingdom by U.K. graduates. No selling price is announced, as the A.U.B.C. is making the pamphlet available to universities and libraries (and to other institutions on request from 36 Gordon Square, London W.C.1).

UTERINE RUPTURE AFTER INTRAMUSCULAR "PITOCIN"

BY

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A case is described of rupture of the pregnant uterus in a patient who was not in labour. Rupture followed upon a medical induction, which included the administration intramuscularly of 5 units of "pitocin" (oxytocin) in two divided doses.

Case Report

The patient, Mrs. P., was a gravida-3 aged 31. Her previous pregnancies had been uneventful, and there was nothing of note in her past medical history.

She was booked for a home confinement. The pregnancy progressed uneventfully until March 5, 1958, when she was one week overdue. A medical induction was therefore given, the sequence of events being as follows:

1 p.m.—2 oz. (57 ml.) of castor oil was given by mouth, followed by a hot bath.

5.15 p.m.—2.5 units of pitocin was injected intramuscularly, followed by an enema.

5.30 p.m.—The enema was returned normally.

5.45 p.m.—A further 2.5 units of pitocin was given.

6 p.m.—The midwife was recalled and the general practitioner notified because the patient had been having very severe lower abdominal pains. She was found to be pale, cold, and sweating; blood-pressure 70 systolic; pulse 80 and of poor quality. Very strong uterine contractions were felt.

6.30 p.m.—The flying squad arrived, and the patient was seen to be desperately ill and clearly bleeding intraperitoneally. As she was too ill to be transferred to hospital, she was rapidly transfused with 2 pints (1,140 ml.) of dextran and 2 pints (1,140 ml.) of group O rhesus-negative blood, oxygen being administered at the same time. Despite these measures her condition did not improve. It was therefore decided that her only chance of survival lay in immediate transfer to hospital, where a laparotomy could be performed immediately.

9.45 p.m.—The abdomen was opened and found to contain 10 pints (5.7 litres) of blood and liquor. A rupture of the left side of the uterus extended from the vaginal vault, through the lower segment, and into the back of the uterus. Because the patient was almost pulseless an intra-aortic blood transfusion was set up and a caesarean hysterectomy performed. Unfortunately she died just before the operation was completed.

Post-mortem Report.—Death was due to shock and to haemorrhage after rupture of the uterus. The laceration in the uterine wall was on the left side; it was about 8 cm. long and extended upwards from the vaginal vault through the lower uterine segment. No other abnormality was found.

Discussion

The reasons for publishing this case history are two-fold. The first reason is because similar cases, when they do occur, are rarely published. A search through the literature has failed to reveal an instance in which uterine rupture has occurred after the administration of intramuscular pitocin in the absence of a scar and before the onset of labour. The second reason is to draw attention to the dangers of undiluted intramuscular injections of pitocin for the induction of labour, and, more particularly, for the stimulation of an inert labour. The fact that uterine rupture did occur before labour became established should serve as an added deterrent to those who would wish to give it for hypotonic inertia.

"Full" medical inductions, as they have been called, are still used extensively both in hospital and in domiciliary midwifery despite the introduction of the oxytocic drip. This is not surprising in view of the fact that some of the most modern textbooks of obstetrics still recommend the reinforcement of the simple medical induction of castor oil, enema, and bath. This reinforcement consists of half-hourly injections of 2.5 units of pitocin until a maximum of six doses have been given, or, alternatively, until labour should start. Unfortunately, as a result of this teaching there are some who look upon the use of pitocin in this way as an accepted practice. It is to be hoped that this article will discourage even those who have used this method for many years and have had the good fortune to avoid a similar catastrophe.

Uterine rupture is not the only danger. There is a very real risk of amniotic-fluid embolus. Wrigley (1959) draws attention to the occurrence of subsequent uterine atony, particularly in the third stage of labour. Furthermore, there is a real chance of producing foetal asphyxia. There is by no means universal acceptance of oxytocic therapy as the choice of treatment for hypotonic inertia. Equally good results can be obtained in the majority of cases by the simple expedient of waiting (Lewis, 1956).

Feeney and Barry (1956), in discussing their series of uterine ruptures, draw attention to the dangers of pitocin and state that great care should be exercised in the use of oxytocin in the grand multigravida. Carey (1959) has listed some important facts concerning intramuscular pitocin, which he says "is frequently ineffective and potentially dangerous." He notes that uterine tone is raised for 10 to 15 minutes in a proportion of cases with doses of 2.5 units, leading to slowing of the foetal heart. Other points which he mentions are the cumulative action of half-hourly injections, the risk of giving an accidental intravenous injection, and the unpredictable response of the patient. In almost all published series the authors emphasize the need for the most careful and constant attention to the patient by an experienced obstetrician.

Chassar Moir (1959) has outlined the work carried out since 1922 to produce a reliable method of standardizing pituitary extract. Despite the introduction of the international unit dosage the action is still so erratic that many obstetricians will use an oxytocin sensitivity test such as that recommended by Nixon and Smyth (1957) before administering a pitocin drip.

The recommended dose of undiluted intramuscular pitocin for induction of labour is generally 15 units in six spaced doses over a period of two and a half hours.

Holmes (1955) has described the use of diluted oxytocin as a continuous intramuscular injection, and states that the average case of hypotonic inertia requires 0.2 units of oxytocin per hour. This figure more than any other should show the danger in administering over ten times this dose in a single injection.

Greenhill (1945), in discussing uterine rupture, stated that a common cause of rupture was the use of pituitary extract but that warnings seemed to be of little use. Ten years later he stated that administration of pituitary extract by intravenous drip was far safer than intramuscular injection (Greenhill, 1955–6).

The danger of producing an amniotic-fluid embolus as a result of the greatly increased uterine contractions has been proved. Barno and Freeman (1959) discussed 15 cases of maternal death due to amniotic-fluid embolus. In seven of these pitocin had been administered, twice by intravenous drip and five times by intramuscular injection.

The use of intramuscular pitocin undiluted, in single or divided doses, for the induction or stimulation of labour should cease. If pitocin has to be used it should be given as an intravenous or intramuscular drip. Owing to the time and attention required by these drips it would seem unlikely that there is any place for them in domiciliary obstetrics. Whenever they are contemplated, it is worth while bearing in mind some of the following contraindications described by Greenhill (1945). Pitocin should never be administered where there is any possibility of obstructed labour, in malpresentation, or after a previous caesarean section. If it is given in labour it should only be for a true hypotonic inertia. It should be avoided in severe toxaemias and should never be used in a patient who has had more than four deliveries. Under no circumstances should a patient be left alone after the administration of pitocin. If contractions are prolonged or too frequent, or there is a change in the foetal heart rate, the administration of pitocin should be stopped, and it may be necessary to give a general anaesthetic in order to diminish the strength of the contractions.

The most recent condemnation of intramuscular pitocin took place at the British Congress of Obstetrics and Gynaecology in July, 1959. To quote Wrigley (1959): "This Congress would render no disservice to the community if it declared its complete condemnation of the practice of administration of pitocin by the method of repeated intramuscular injections."

Summary

A case is described of uterine rupture followed by maternal death. Rupture occurred shortly after a medical induction which included two intramuscular injections each of 2.5 units of "pitocin" (oxytocin). The dangers of such treatment are discussed and a plea is made for the abolition of single or spaced injections of pitocin for the induction of labour and for the stimulation of hypotonic inertia.

I am indebted to Mr. Gwilym Evans for permission to publish this case.

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Mr. JOHN DODD, as honorary secretary of the British Hospitals Contributory Schemes Association, has accepted invitations from a number of medical, social service, and public administration graduate schools in American universities, including Columbia, New York, and Cornell, to lecture on the survival of voluntary effort in Great Britain under State medicine. Mr. Dodd will take part in discussions on medical care with faculty members and students, and will address some leading Blue Cross organizations in the eastern States.

IN VITRO INVESTIGATIONS OF TWO TYPES OF LUPUS ERYTHEMATOSUS PLASMA FACTOR

BY

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AND

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Our previous experiments on dog and man confirmed the probable existence of two types of lupus erythematosus plasma factor, one transferable and one non-transferable (Bencze *et al.*, 1959). As proved by further studies, it is not the amount transfused which accounts for the incidence of the two types of lupus erythematosus plasma factor (Bencze *et al.*, 1960).

This paper reports on *in vitro* investigations with the lupus erythematosus (L.E.) cell. In comparative tests the patient's and a normal subject's leucocytes were added to plasma obtained from several patients with systemic lupus erythematosus (S.L.E.) in order to find out whether any difference could be detected *in vitro* between the two types of plasma factor.

Methods

S.L.E. Plasma + Patient's leucocytes.—Blood was taken under sterile conditions (with heparin added) from S.L.E. patients; the examination for L.E. cells was made by Zinkham and Conley's (1956) rotation method. This was used as the control test.

S.L.E. Plasma + a Normal Subject's Leucocytes.—A known amount of plasma obtained from S.L.E. patients was added to a normal subject's leucocytes (blood was taken from normal individuals under sterile conditions and heparin added, the layer of white blood cells being pipetted off). Examination for L.E. cells was by the rotation method of Zinkham and Conley.

S.L.E. Plasma Transfer Experiment.— By methods described in earlier publications, plasma from cases of S.L.E. was transfused into patients with neoplastic diseases and into dogs (Bencze *et al.*, 1958; Bencze and Ludányi, 1960).

Results

Examination for L.E. cells were made on several occasions and at different times with plasma obtained from 16 S.L.E. patients, adding to the plasma the patient's own or a normal subject's leucocytes. Many L.E. cells were observed in all 16 patients when their own leucocytes were used. The results of our *in vitro* L.E.-cell investigations are listed in the Table, and the results of *in vitro* and *in vivo* experiments are compared.

Discussion

Eight samples of S.L.E. plasma (non-transferable type) were treated *in vitro* with leucocytes of normal subjects. No L.E. cells were found when the plasma of three S.L.E. patients was treated with leucocytes of normal subjects; many L.E. cells, however, could be found in every case when the patient's own leucocytes were added to the plasma. With the other five samples of

Comparative L.E. Cell Investigations with Patient's own and Normal Subject's Leucocytes

Case No.	Initials	Lupus Erythematosus Cell *In vitro*					*In vivo* Plasma Transfer Experiment
		Patient's Own Leucocyte	Normal Subject's Leucocytes S.L.E. Plasma in ml.				
			0·25	0·5	1·0	2·0	3·0	
1	T.J.	++++	0	0	0	0	0	N.T. (1)
2	K.E.	++++	++++	++++	++++	++++	++++	T. (2)
3	V.M.	++++	0	0	±	±	±	N.T. (4)
4	M.K.	++	0	0	0	0	0	(0)
5	P.J.	++++	0	0	0	±	±	N.T. (4)
6	K.L.	++++	++++	++++	++++	++++	++++	(0)
7	O.P.	++++	++++	++++	++++	++++	++++	T. (20)
8	B.I.	++++	0	0	±	±	±	N.T. (8)
9	T.I.	++++	++++	++++	++++	++++	++++	T. (9)
10	K.K.	++++	0	0	0	0	±	N.T. (3)
11	S.M.	+++	0	0	0	0	0	N.T. (2)
12	P.J.	++++	0	0	0	0	0	(0)
13	K.F.	++++	++++	++++	++++	++++	++++	T. (4)
14	H.K.	+++	0	0	0	0	0	N.T. (2)
15	P.J.	++++	++++	++++	++++	++++	++++	T. (4)
16	P.F.	++++	0	0	±	±	±	N.T. (4)

± = Examinations showed in some cases presence in others absence of L.E.-cell. T. = Transferable. N.T. = Not transferable. Figures in parentheses indicate number of experiments.

S.L.E. plasma of non-transferable type considerably fewer L.E. cells were seen when a normal subject's cells were added than when the patient's own leucocytes were added, even when more plasma (2 and 3 ml. respectively) was used. At the same time, we failed to produce L.E. cells with smaller amounts (0.25 and 0.5 ml.) of S.L.E. plasma. *In vitro* investigations were carried out at different times on several occasions with plasma of these five S.L.E. patients, but we failed to find L.E. cells in some cases when a normal subject's leucocytes were added—even when as much as 3 ml. of plasma was used.

The L.E.-cell phenomenon could not be produced with the plasma of five S.L.E. patients out of a total of 16 when a normal subject's leucocytes were added (no transfer experiment was completed with the plasma of two S.L.E. patients). Significantly fewer L.E. cells could be detected when the plasma of a further five S.L.E. patients was treated with a normal subject's cells than when the patient's own leucocytes were added. But when the plasma of five S.L.E. patients which proved to be transferable was treated *in vitro* with leucocytes from normal subjects (on several occasions and at different times) the L.E.-cell phenomenon was always observed—as it was in Case 6, in which no plasma transfer experiment has been completed. The number of L.E. cells produced (compared with the total number of leucocytes) was the same whether the patient's own or a normal subject's leucocytes were added *in vitro* to samples of plasma from these six S.L.E. patients. The L.E.-cell phenomenon came into being in all six cases when only as little as 0.25 ml. and 0.5 ml. of plasma was used.

Ten of the 16 S.L.E. patients were systematically observed by us for a period of years. L.E.-cell examinations were frequently made on different occasions —six times at least. In six of these 10 patients (Cases 1, 4, 5, 10, 14, and 16) no L.E. cells could be found by Zinkham and Conley's method on several occasions, even when the patient's own leucocytes were used. Plasma transfer experiments were completed on five of six S.L.E. patients; all five proved to be non-transferable. In the other four S.L.E. patients L.E. cells could always be found (Cases 6, 7, 9, and 13); in three of these four patients *in vivo* plasma transfer experiments were completed, and all three proved to be transferable. [We wish to make it clear that comparative *in vitro* investigations were made only in those cases in which the L.E.-cell phenomenon could be produced with the patient's own leucocytes.]

Summary

Comparative *in vitro* investigations using the leucocytes of S.L.E. patients and of normal subjects provided evidence that a difference existed between the transferable and non-transferable type of L.E. plasma factor. In the latter type L.E. cells could be produced *in vitro* only when the patient's own leucocytes were used; they could not be produced—or could be produced only in very small numbers—with the leucocytes of normal subjects.

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Medical Memoranda

Case of Listeria Meningitis

Neonatal meningitis due to *Listeria monocytogenes* is rare enough to raise difficulties in diagnosis and treatment. Human listerial infection may be more common than generally supposed, and papers reporting cases from Great Britain support this view (Edmunds, Nicholson, and Douglas, 1957; Mair, Mair, Stirk, and Reid, 1957; Barrow and Pugh, 1958; Turner, Dawson, and Pryce-Jones, 1958).

CASE REPORT

The patient, a white male infant, was born by spontaneous vertex delivery after an uneventful full-term gestation. Birth weight was 6 lb. 14 oz. (3,120 g.). Progress was normal for the first 10 days; he then had loose bowel motions and became febrile. He was admitted to the 7510th U.S.A.F. Hospital, Wimpole Park, two days later.

On the day of admission he appeared lethargic and showed opisthotonos. The temperature was 100.4° F. (38° C.); there were no other physical signs. Lumbar puncture and blood culture were performed. The cerebrospinal fluid was turbid and contained 2,400 leucocytes per c.mm. (90% polymorphonuclear), the sugar was 26 mg. and protein 440 mg./100 ml. The Gram film showed a moderate number of

Gram-positive bacilli, mainly extracellular in position, at first thought to be *Haemophilus influenzae*, in view of the ease with which they could be decolorized, but subsequently identified as *Listeria monocytogenes*. Similar organisms were isolated from the blood culture after 48 hours' incubation. The organism was resistant to penicillin but sensitive to tetracycline, erythromycin, streptomycin, chloramphenicol, and sulphonamides. The haemoglobin was 17.5 g./100 ml., white-cell count 15,800/c.mm. (36% polymorphonuclear leucocytes, 60% lymphocytes, 4% monocytes).

Treatment was started with intravenous fluids. Crystalline penicillin, 400,000 units intramuscularly, chloramphenicol, 75 mg. intramuscularly, and sulphadiazine, 150 mg. subcutaneously, were given six-hourly. Penicillin was stopped on the second day and the chloramphenicol and sulphadiazine were given orally after three and five days respectively. Intravenous fluid was discontinued after two days.

The child made an excellent response to treatment. On the third day he was apyrexial and started to gain weight; there were no abnormal physical signs five days after admission, and chloramphenicol and sulphadiazine were discontinued.

Lumbar puncture was repeated at the end of the third week of the illness, the C.S.F. was sterile, the sugar 44 mg. and protein 150 mg./100 ml. Further progress was interrupted by a mild chest infection, but the child was discharged apparently well and gaining weight after five weeks in hospital.

Morphology.—The organism on first isolation was a small, short, Gram-positive rod resembling a diphtheroid bacillus. Some V forms were present. It could be easily made to appear Gram-negative by decolorization with acetone. Filamentous forms appeared after repeated subculture.

Cultural Characteristics.—Growth occurred fairly well on a variety of solid media. On blood-agar incubated at 37° C., slightly opaque, smooth domed colonies, less than 1 mm. in diameter, were visible after 18 hours. After 48–72 hours the colonies were 2–3 mm. in diameter, milky in appearance, and with fimbriate edges. A narrow zone of clear (beta) haemolysis was present around the colonies on blood-agar. The presence of a soluble haemolysin was confirmed by the method of Webb and Barber (1937). On blood tellurite, minute black colonies were just visible in 18 hours; no growth was apparent on MacConkey's medium after 36 hours. After repeated subculture "rough" colonies (Barber, 1939) could be distinguished.

Motility.—The tumbling motility said to be typical of *Listeria monocytogenes* could be seen in glucose-broth cultures grown at room temperature for 18 hours.

Biochemical Reactions.—The organism produced acid but not gas from maltose, glucose, xylose, and salicin within 36 hours and from lactose and sucrose in five days. Dulcite and mannitol were not fermented. Urea was not split on Christenson's medium; hydrogen sulphide and indole were not formed. There was no growth in Koser's citrate, the methyl-red test was positive, and the Voges–Proskauer reaction negative.

Antibiotic Sensitivities.—Strips of filter-paper, soaked in solutions of antibiotics, incorporated in nutrient agar, were used for testing antibiotic sensitivities. Organisms of known sensitivity were used as controls.

Production of Monocytosis in Rabbits.—The conjunctival sac of one eye of each rabbit was infected with a swab dipped in an 18-hour glucose-broth culture. The blood monocytosis in two rabbits is shown in the Table. After recovery from the conjunctivitis, the rabbit conjunctival test was performed on one rabbit and local immunity demonstrated (Julianelle, 1941).

Monocytic Response in Rabbits to Listeria Monocytogenes

Date	Rabbit 1		Rabbit 2	
	Total W.B.C./c.mm.	Monocytes/c.mm.	Total W.B.C./c.mm.	Monocytes/c.mm.
3/2/59	10,000	750	6,000	450
4/2/59, conjunctival inoculation	8,000	760	7,000	630
6/2/59	9,000	1,350	9,000	990
8/2/59	11,000	1,760	8,000	1,840
10/2/59	15,000	2,850	8,000	1,680
12/2/59	10,000	1,200	8,000	1,400

Serology.—A rabbit antiserum of a titre of 1/2,000 to a known strain of *Listeria monocytogenes* agglutinated a formolized suspension of the organism at 1/1,000.

Serological Investigations of the Patient's and Mother's Serum.—No agglutinating or complement-fixing antibodies to formolized suspensions of the organism were detected on sera taken from the patient on the 11th and 25th days of the illness or in the mother's serum 37 days after delivery. The patient's serum gave a negative Paul–Bunnell reaction. Dr. D. G. Ingram determined the immuno-conglutinin titre of the patient's and the mother's serum. No activity was detected in the mother's serum, but the second serum from the patient showed a significant rise in titre compared with the first, indicating that an antibody response had occurred.

COMMENT

Listeria monocytogenes has been confused with streptococci, pneumococci, diphtheroids, and *E. coli*. In this case, as in that described by Selinger and Becker (1955), the ease with which the organism could be decolorized led to a provisional diagnosis of *H. influenzae* meningitis. Penicillin therapy was therefore discontinued. Fortunately, treatment with chloramphenicol and sulphadiazine was remarkably effective.

Though this case is an exception, resistance to penicillin seems to be uncommon. Of six cases described in Great Britain within the last three years the organism was found to be sensitive to penicillin in five, and in the United States *Listeria monocytogenes* appears to be more often sensitive to penicillin than to chloramphenicol (Dedrick, 1957).

We thank Captain Thomas L. Evans, U.S.A.F., for the clinical details of this case, and Dr. D. G. Ingram, late of the department of pathology, University of Cambridge, for determining the immuno-conglutinin titre and supplying the antiserum.

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Arthrodesis of the Great Toe

Keller's operation is still the most frequently performed operation for hallux valgus and rigidus. The results are often good, but they are not reliable. In my view the main reason for this is that metatarsalgia is often not relieved. In the normal foot the weight taken by the forefoot is divided mainly between the metatarsal heads and the tip of the great toe. The other toes take a relatively small proportion of the weight. In a severe hallux valgus the great toe deviates so far laterally that its tip takes only a little weight and the metatarsal heads

take the greatest part. This I believe to be the main cause of metatarsalgia. Only if Keller's operation is successful in restoring both the normal position and the mobility of the great toe will it relieve metatarsalgia. If Keller's operation is done on a very severe hallux valgus where there is a much broadened forefoot with metatarsal prolapse and callosities the result is often a great toe still deviated laterally and upwards, with little power of active flexion, even though passive movements are quite good. In such a foot only the local pain from the first metatarsal exostosis is relieved but not the metatarsalgia.

I have reviewed an earlier series of 75 cases of hallux valgus and rigidus in which Keller's operation was performed 109 times. In 20 feet there was persistent metatarsalgia of varying degree. Bonney and McNab (1952) report a high incidence of metatarsalgia persisting after Keller's operation.

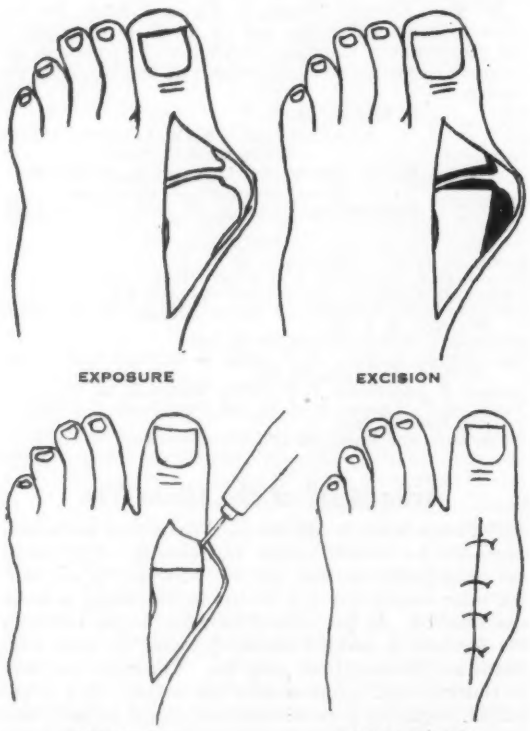
Arthrodesis of the first metatarsophalangeal joint is a logical operation in hallux rigidus. It was often observed that when a hallux rigidus became completely stiff the pain disappeared. It is also effective in hallux valgus, because it corrects the defective weight distribution. When the great toe is arthrodesed in a satisfactory position its tip takes the normal proportion of the weight again and relieves the metatarsal heads.

Various methods of arthrodesis for the first metatarsophalangeal joint have been put forward. They have not become popular because they are too time-consuming and make the operation a relatively major undertaking.

Operation

A small pair of bone-cutting forceps, a Watson-Jones guide-wire handle, a small round punch, and a Pidcock check pin are needed in addition to the usual instruments for Keller's operation. The incision is a straight dorsal one, just medial to the long extensor tendon. The distal half of the first metatarsal and most of the proximal phalanx are exposed subperiosteally (see Fig.). The exostosis on the metatarsal head is removed, leaving the adventitious bursa in place. The joint surfaces on the metatarsal head and the base of the proximal phalanx are then excised, leaving two flat congruous cancellous surfaces. The joint under the metatarsal head with the sesamoids must be preserved. The toe is held in the correct position. The Pidcock pin held in the Watson-Jones handle is used to transfix the base of the proximal phalanx and the metatarsal head obliquely (see Fig.). The Pidcock pin is then hammered home, using the small punch. Firm fixation is obtained. The wound is sutured in two layers.

The correct position is with the toe in about 10 degrees valgus (see Fig.) and 20 degrees dorsiflexion. If the toe is arthrodesed exactly in line with the first metatarsal it is difficult to get well-fitting shoes with a straight inner border. 20 degrees of dorsiflexion is quite sufficient for wearing shoes with a medium heel, but it is essential to warn ladies that they cannot wear a very high heel.



After-treatment

No splinting is required during the first fortnight, when the patient is in bed. A below-knee walking-plaster is then applied, including the great toe. This is worn for another four weeks. Fusion is then usually complete.

Patients should be warned that it takes about three months to get a good result. For about six weeks after the plaster is removed the foot is rather swollen, walking is awkward, and shoes are difficult to fit. This is really no longer than convalescence after Keller's operation.

Results

During a period of three years 110 operations were done for 72 patients ; 38 were bilateral and 34 unilateral. Nine operations were for hallux rigidus, two for failed Keller's operation, and all the others for hallux valgus. Sex and age distribution was as expected, with a large preponderance of women between 40 and 60, but seven patients were between 20 and 30 and one was over 70.

I have classed results as good in 100 feet, fair in 9, and poor in 1. This one was due to a late wound infection (the only one) causing non-union and recurrence of the deformity. Twenty-four patients had metatarsalgia before operation, and afterwards six patients still had metatarsalgia in seven feet. In two feet the toe had been arthrodesed in line with the first metatarsal instead of in 10 degrees valgus and there was pressure from shoes. Fusion failed in five feet: in two of them the operation was repeated successfully ; two more had a trouble-free short fibrous ankylosis. In 18 feet the pin loosened and was extruded. It either penetrated the skin spontaneously or was removed under local anaesthesia. This is not a serious disadvantage ; in fact, there was no other wound infection.

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Reviews

PAEDIATRIC PATHOLOGY

Pathology of Infancy and Childhood. By Agnes R. Macgregor, M.D., F.R.C.P.Ed., F.R.C.O.G. (Pp. 631+viii; illustrated. 75s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

It is a pleasure to read this book on paediatric pathology by Dr. Agnes Macgregor, of Edinburgh. No one in the British Isles has had the experience which she has had, and in this book she has compressed many years of experience into a volume of compact size. The book is beautifully printed on good paper, with numerous excellent and clear illustrations.

The book begins with 113 pages on the foetal and neonatal periods, and these are followed by 132 pages on congenital malformations. Other sections include infective diseases, the effect of poisons and accidents, and other important aspects of paediatric pathology. There are references at the end of each chapter, without, unfortunately, the titles of the papers.

This is a book which all concerned with the care of children will want to have. It will be particularly useful for pathologists who deal with limited numbers of children.

R. S. ILLINGWORTH.

HYPERTENSION AND PREGNANCY

High Blood Pressure and Pregnancy. By Lance Townsend, M.D., B.S., F.R.C.S.(Edin.), F.R.A.C.S., F.R.C.O.G., D.T.M.&H. (Pp. 115+viii; illustrated. 40s.) Melbourne: Melbourne University Press. London: Cambridge University Press. 1959.

The University of Melbourne awarded a Doctorate of Medicine to Professor Townsend for his thesis on high blood-pressure and pregnancy. The Melbourne University Press then published it, thus making a highly successful "double" on which the professor deserves hearty congratulations. The price of 40s. for this little book of 115 pages may have a temporarily hypertensive effect on some buyers, but if the bookseller would accept Australian currency the change from two English pounds would purchase an initial supply of the hypotensive drugs which Professor Townsend recommends.

An excellent critical review of British and American literature on hypertension, particularly in reference to pregnancy, will delight postgraduates reading for higher degrees. The views of Pickering, Browne, Theobald, Keller, and American workers including Dieckmann, Chesley, Taylor, and Reid, are admirably summarized. The problem Professor Townsend planned to investigate was the effect of bed rest, hypotensive drugs, and "anti-pre-eclamptic measures" on high blood-pressure in pregnancy. With the co-operation of colleagues at the Royal Women's Hospital, Melbourne, 101 hypertensive patients were placed under his personal care and were delivered in 1956 (p. 27). On p. 29 we read: "In the 1956 series *it so happened* that all the patients (the 101) were seen before the twelfth week" (the italics are the reviewer's). This is an important fact, and makes it clear that the material studied was highly selected, thus adding to the value of the investigation. It is surprising, therefore, that the author should not make clearer the exact nature of the material he proposed to study in his initial outline of his experiment. One hundred and one patients hypertensive in the first trimester is a considerable clinical material, but the Royal Women's Hospital is a large and famous institution where 6,866 booked patients were delivered in 1956. The summary (p. 110) states: "In 1956, 101 patients with high blood-pressure were delivered." As 101 presented with hypertension in the first trimester it would follow that the remaining 6,765 proceeded to delivery without hypertension. This cannot be correct unless the author uses the term hypertension in pregnancy to refer only to the highly selected group with hypertension in the first trimester. In a small but valuable contribution such as this the reader should not be forced to search from page to page trying to discover what the author means. There is further confusion. "The important factor in producing a small baby is the height of the blood-pressure at the end of pregnancy, especially if this is associated with proteinuria—that is, if pre-eclampsia has developed" (p. 91). Professor Townsend is discussing a highly controversial subject, and it is the more important, therefore, that his views should be expressed clearly. The words quoted cannot mean what they appear to mean, for by the end of pregnancy the size of the baby has already been determined. "In patients who commence pregnancy with high blood-pressure small babies are more commonly found in those with very high diastolic pressures associated with proteinuria at the end of pregnancy" (p. 113). This is a statement as commendably clear as the earlier one is confusing.

Professor Townsend emphasizes the importance in his series of an initial high diastolic pressure, particularly in relation to foetal prognosis. Using this yardstick and comparing the control series of 1946 to 1947 with the 1956 series it is found that 22% of the 1956 series had a diastolic pressure of 100 or more, compared with 40% in the controls. Here again, however, there is confusion. The text refers repeatedly to 101 patients in the 1956 series, while Table 25 gives the number as 105. Similarly, in the 1946 to 1947 series (Table 25) the numbered delivered is 92, whereas in Table 26 it is 94. Whichever total is correct the evidence available suggests that the number of severe hypertensives in the 1956 series was proportionately less than in the control series. This fact is important when endeavouring to assess the results of treatment. None the less, the maternal and foetal results achieved are most encouraging, and are a tribute to the high standard of care these patients received.

In spite of the above criticisms this little book is well worth reading. Until the second edition is published, and he has an opportunity of correcting confusion in text and tables, Professor Townsend may often be misquoted.

J. STALLWORTHY.

HUMAN BIOCHEMICAL GENETICS

Ciba Foundation Symposium, Jointly with the International Union of Biological Sciences, on Biochemistry of Human Genetics. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. (Pp. 347+xii; illustrated. 50s.) London: J. and A. Churchill, Ltd. 1959.

An exciting stage has now been reached in human biochemical genetics where the chemical nature of gene action is becoming recognized. Some of the foremost workers in this field met in 1959 in Naples for a symposium organized jointly by the Ciba Foundation and the International Union of Biological Sciences. L. S.

Penrose surveyed the genetical analysis of man: technical methods of family study and the human chromosome map. Not all the specific contributions can be mentioned here; they included lectures on hereditary galactosaemia (H. A. Kalckar), pseudo-cholinesterase variants (W. Kalow), primaquine sensitivity of red cells (B. Childs and W. H. Zinkham), plasma proteins (H. Harris), haptoglobins (O. Smithies). Blood groups are discussed by W. T. J. Morgan and W. M. Watkins, and haemoglobins by H. A. Itano and V. M. Ingram and his colleagues. General considerations are discussed by R. Ceppeliui and S. Brenner.

This is an impressive collection of up-to-date information from a widespread field here conveniently gathered together. Of particular interest are the discussions, of which the most important is perhaps that on the cistron, a genetical unit which is smaller than the chromosome and comprises a group of closely linked genes. It is here that work on micro-organisms has been blazing the trail and is now followed closely by that on blood groups and haemoglobins.

H. LEHMANN.

PEPTIC ULCER MONOGRAPH

The Physiology and Treatment of Peptic Ulcer. Edited by J. Garrott Allen, with 11 contributors. (Pp. 236+x; illustrated. 56s. 6d.) Chicago: University of Chicago Press. London: Cambridge University Press. 1959.

This monograph was planned for the occasion of Dr. Dragstedt's retirement (but without his prior knowledge) and was written by twelve of his past or present associates.

Chapters cover such subjects as the cephalic phase of gastric secretion, the physiology of the antral phase of secretion, medical management, and surgical procedures for duodenal ulcer.

As a graceful tribute to a most distinguished American surgeon and scientific investigator the monograph is admirable. But such monographs can remain of special interest only to those actively working in this field of research and they are of little value to the general physician and surgeon. This is because of the overall lack of balance. There is very little indeed about surgery for gastric ulcer; again, no general reader will be interested in a whole chapter on the technique of *x*-raying patients and in the photographs of control panels.

F. AVERY JONES.

MEDICAL EDUCATION DISCUSSED

Report of the First Institute on Clinical Teaching. Edited by Helen Hofer Gee and Julius B. Richmond, with the assistance of the Planning Committee. Editorial co-ordination by E. Shepley Nourse. Part 2. (Pp. 233+xxx. $2.) Evanston, Illinois: Association of American Medical Colleges. 1959.

For most of the post-war years the Association of American Medical Colleges has held a "Teaching Institute," which may briefly be described as a well-organized working party of competent representatives of all medical schools in North America concentrating upon one facet of medical education. Much relevant data is collected over the preceding twelve months, sifted, and presented for the members to study during a three- or four-day meeting. No one who has attended an Institute can fail to be impressed with its value to the individuals present, to the schools from which they come, and to the gradual solution of the problems of medical education.

The published reports, shorn of much of the round-table discussions of small groups of informed and interested participants, seldom do justice to the meetings. Nevertheless, they invariably contain much of value to the reader, both in regard to opinion and to fact, even if he is not conversant with the American scene. This particular Institute in 1958 was the first of two devoted to clinical teaching. The main topics are the objectives of clinical teaching, the setting of clinical teaching, and the student, the patient, and the teacher. The views expressed on the functions of teaching hospitals will be of considerable interest to British readers.

JOHN ELLIS.

IMPOTENCE

Sexual Impotence in the Male. By Leonard Paul Wershub, M.D., F.A.C.S., F.I.C.S. Foreword by Ralph E. Snyder, M.D. (Pp. 126+xiii; illustrated. 46s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The author of this book is a urologist, and, though Dr. Wershub emphasizes that in 90% of patients complaining of impotence the disorder is of psychological or functional origin, the 10% of cases due to organic causes are given 43 pages as against 31 for the chapter on functional causes. In other words, the point of view of the urologist prevails. This is well illustrated by the opening remarks in chapter 8: "Of all cases of sexual impotence in the male, something like ninety per cent. is functional and only approximately ten per cent. is actually due to organic cause. Therefore, it is a *must* for the physician to determine *first* whether the condition complained of is organic. . . ."

An aphorism of one of my clinical teachers was, "The commonest diseases occur most often," but Dr. Wershub, the urologist, considers that all patients complaining of impotence should first go through the rigmarole of urological investigation to look for the 10% of uncommon causes before he is prepared to accept the likelihood of the commonest cause occurring most often in one of his patients. To complicate the issue, he agrees that the mere finding of a minor urological abnormality does not by any means indicate that it is the cause of the complaint of impotence. Surely urological examination, like any other special investigation, must be advised on the merits of the individual case and not as step one in all cases.

In spite of this criticism the book gives an interesting and full survey of the causes of impotence in the male, though it has relatively little to say about the treatment of the disorder except in general terms. There are a large number of spelling and grammatical errors, but otherwise the standard of production is high. The bibliography, covering 174 items, is a useful feature and there is a good index.

G. I. M. SWYER.

CHEMICAL FIGHT FOR THE MIND

A Pharmacologic Approach to the Study of the Mind. Edited by Robert M. Featherstone, Ph.D., and Alexander Simon, M.D. (Pp. 399+xxviii; illustrated. 86s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publicauons. 1959.

The marketing of some of the newer drugs in the treatment of mental illness is now highly competitive, but it can also be very rewarding. Drug manufacturers are therefore always developing new techniques of advertising their wares, and this sort of book is one of them. A conference is organized in some part of Europe or America, officially sponsored perhaps by a

university or medical school, and eminent persons are invited to read papers. Expenses of the congress are met by a particular drug firm, and a special book or a number of a journal is later published, and a group of papers are included in it about the particular new drug being put on the market. Some eminent workers were collected for this symposium and a wide variety of topics was discussed. Some old ground was covered, but there are some interesting round-table discussions reported between workers in the many varied disciplines now being mobilized in the chemical fight for the mind of man. The reviewer must be forgiven for not giving this particular anti-depressant drug any further publicity by naming it. And at least some of those reporting on the clinical value of the particular amine-oxidase inhibitor being boosted seemed to have been rushed too readily and early into print, the papers on it falling generally below the standards of the rest of the book.

One of the best parts of the book is a talk given by Aldous Huxley, appealing to scientists to meet ordinary intelligent laymen from time to time to discuss their findings so as to " make the best of both worlds. The best of the purely human world, and the best of this extraordinarily wonderful and terrifying world of technique."

WILLIAM SARGANT.

CHILD PSYCHOPHARMACOLOGY

Child Research in Psychopharmacology. Organized and edited by Seymour Fisher, Ph.D. Foreword by R. H. Felix, M.D. (Pp. 216+xvi. 52s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

This book describes the proceedings of the Conference on Child Research in Psychopharmacology held in October, 1958. It was sponsored by the Psychopharmacology Service Center of the National Institute of Mental Health. The main emphasis of the conference was laid on a methodical approach to the research problems of, and the development of new ideas for, psychopharmacological research. The proceedings have been subdivided into the following chapters: basic issues in drug research with children; opportunities and limitations of a paediatric age group, by Leon Eisenberg; basic problems involved in the use of the newer neuro-pharmacological drugs in childhood, by Reginald S. Lourie; populations, behaviours, and situations; some ecological considerations in child drug research, by Lloyd J. Borstelmann; the collaborative study as a possible technique for child research in psychopharmacology, by Stewart H. Clifford; techniques of behaviour study for children, by Boyd R. McCandless; the use of operant conditioning techniques in children, by Eugene R. Long; comparative drug-behaviour analysis, by Sherman Ross; and some neurophysiological problems relevant to chemical intervention in the growing organism, by Lila Ghent.

The first chapter of the book contains a very useful synoptic review of psycho-active drugs written by Jonathan O. Cole and C. J. Carr. The authors have made a critical survey of tranquillizers, non-barbiturate calmatives and sedatives, and anti-depressive agents. They realize that the usefulness of most of the components of these agents has yet to be assessed in a well-controlled study. The last chapter contains a reference list of 159 papers written in the English language and dealing with the use of psychopharmacological agents in treating children; it is compiled by L. Bouthilet and S. Fisher. This reference list is followed by a very helpful subject index.

The speakers were not professional pharmacologists, but mainly psychologists, psychiatrists, or paediatricians. Their free confession of general ignorance in the field stimulated some very fruitful discussions, and it is extremely interesting to note the very different approaches to research of the various members of the conference. Many of the lecturers deal with the design of research projects, the standardization of selection of patients and controls, testing procedures, evaluation of data, and follow-up studies. Loretta Bender, however, who has gone through many years of frustration in this research field, claims, " We cannot fool ourselves by designing standardized medical research and matching controls among human beings, especially children . . . every child is unique . . . when we try to match two children we introduce an error which we are inclined to forget later." The reviewer is of the opinion that during this conference too little attention was paid to the somatic components, to retarded and precocious development in childhood, and, as a result, to the different ways in which even so-called " matched children " react to drugs.

Nevertheless, this conference was the first attempt, and a very interesting one, to study methodological approaches and new ideas in a still very young research field. There is no doubt that every professional worker interested in the action of psychopharmacological drugs on children will benefit from a careful study of this book.

MAX REISS.

MEDICAL GYNAECOLOGY IN AMERICA

Fundamentals of Gynecology. By Samuel J. Behrman, M.B., Ch.B., M.S., M.R.C.O.G.(Lond.), F.A.C.S., and John R. G. Gosling, M.D. (Pp. 416+xii; illustrated. 76s.) New York, London: Oxford University Press. 1959.

It is always interesting to study how the different branches of medicine are presented in other countries, and particularly when, as in this case, it is done by very competent teachers. This book is largely concerned with procedures which can be done in the consulting room, and mere indications are given of necessary major surgical operations. It is divided into seven parts: " Anatomical Considerations "; " Menstrual and Endocrine Considerations "; " Inflammations "; " Benign Tumours "; " Malignant Neoplasms "; " Conditions Related to Conception "; and " General Principles." It is somewhat surprising that 164 of the 403 pages should be devoted to inflammations and tumours and only 30 pages to anatomy, and these are sketchy and not always strictly accurate.

Some differences in terminology are noted, but the fundamental difference in outlook between the authors and British opinion is revealed on page 1, where it is dogmatically asserted that " Good medical practice should recommend routine pelvic examination, commencing in the prepubertal years and continuing throughout the patient's life." May the two outlooks never merge. The information imparted in an empirical manner is very considerable, but the sections are uneven. That on menstrual and endocrine considerations is outstandingly good, whereas that on general principles is most inadequate. Many of the illustrations are original drawings which do in fact show what is meant. The index is not so helpful as it might be. The format is good and no misprint was noted.

Your reviewer enjoyed reading this book but finds it difficult to imagine its appeal in this country. It is not designed for examination purposes, and, although medical students would profit by reading it, other books would suit them better. It is clearly meant for general practitioners who practise medical gynaecology, as in France, of whom there are few in this country.

G. W. THEOBALD.

BEDSIDE BOOK

The Surgeon's Log. By J. Johnston Abraham. Seventh edition. (Pp. 244+xii; illustrated. 18s.) London, Melbourne, Toronto: Heinemann. 1959.

The Surgeon's Log has for almost fifty years been a best-seller, and seems well set for another similar period. Wherein lies the charm? It is, of course, well written, but many well-written books do not sell well. It is full of interesting facts about the various Eastern countries visited, but merely factual travel-books *can be* deadly dull. It contains many good stories, but those alone would not account for a sale of half a million copies. I have read the book several times and each time have found it delightful. Why?

Because the author not only has the gift of telling a good story well, but possesses, in addition, the rare power of conjuring up a lifelike scene by a few deft touches of his word-artistry. Reading this book is like going round a pleasing picture gallery with a guide who amuses and instructs with stories about each picture. It is an ideal bedside book. Yet we are told that eight publishers refused this gold-mine before a good judge of books wisely accepted it, and, incidentally, gave it the present attractive title.

ZACHARY COPE.

Though popular expositions of atomic physics, relativity, and quantum mechanics are fairly plentiful, much less is available to tell the layman about recent biological discoveries. To help fill this gap Dr. J. A. V. Butler, F.R.S., has written *Inside the Living Cell* (George Allen and Unwin; pp. 174; 21s.). Though the blurb on the jacket says that the author uses non-technical language to describe the advances which have been made in the last 10 years, the author himself in his preface does rightly admit that "many names are inevitable." Nor is he likely to find that readers are deterred by this. The intelligent layman enjoys wading through unfamiliar technicalities. The fact is that a great many people enjoy learning about something unfamiliar, and are willing to make the effort to do so in the only way possible—that is, through first learning something of the vocabulary of the subject. This interesting and informative book touches on much recent biological work, including such subjects as nuclear chemistry, cellular genetics, viruses, antibodies, and cerebral function. It would give a sixth-former inspiration or a stockbroker relaxation. There is much of interest, too, for medical men who want to know something about modern biological research.

The science of radiology has made enormous advances since the last edition in 1950, says the preface to the third edition of *A Textbook of X-ray Diagnosis* by British authors in four volumes—the present volume, volume 4, covers bones, joints, and soft tissues—and only an encyclopaedic work could hope to keep up with the rapid changes in radiological observations and techniques. The editors' aim is more modest: the volumes were conceived as a textbook "to describe fundamental principles in interpretation and relate them to the day-to-day clinical problems of the average *x*-ray department"; and they reflect, as did previous editions, the best current practice of radiology. (H. K. Lewis & Co., Ltd.; 714+xvi pp., 735 figs., £5 10s. net.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

First Canadian Symposium on Non-Gonococcal Urethritis and Human Trichomoniasis. Montreal, 1959. Edited by Zoltan Gallai and Lucien Sylvestre. (Pp. 434; illustrated.) Basle, New York: S. Karger. 1960.

Dear Dead Days. A Family Album. By Charles Addams. (Pp. 125; illustrated. 18s.) London: Paul Hamlyn. 1960.

The Seven Ages of Woman. By Elizabeth Parker, M.D. Edited by Evelyn Breck. (Pp. 609+x. 30s.) London: Darton, Longman and Todd. 1960.

Herzschall-Fibel. Einführung in die Mechanokardiographie. By Professor Dr. K. Holldack and Dr. D. Wolf. (Pp. 101+xii; illustrated. DM. 16.80.) Stuttgart: Georg Thieme Verlag. 1960.

Internationales Biguanid-Symposium. May 12 and 13, 1960, in Aachen. Edited by Professor Dr. F. Bertram and Dr. G. Michael. (Pp. 167+viii; illustrated. DM. 16.80.) Stuttgart: Georg Thieme Verlag. 1960.

Pathologische Reaktionen der Persönlichkeit. Neurosen und Psychogene Psychosen. By Professor Dr. Nikola Schipkowensky. Part I. (Pp. 210. 84s.) Vienna, Bonn, Berne: Wilhelm Maudrich Verlag. 1960.

Man's Presumptuous Brain. An Evolutionary Interpretation of Psychosomatic Disease. By A. T. W. Simeons, M.D. (Pp. 281+xii; illustrated. 25s.) London: Longmans. 1960.

Doctor Agnes Bennett. By Cecil and Celia Manson. Foreword by J. C. Beaglehole. Epilogue by Agnes Bennett, O.B.E., M.D.(Edin.), B.Sc.(Syd.). (Pp. 189+xv. 18s.) London: Michael Joseph. 1960.

A Textbook of Gynaecology. By K. M. Masani, M.D.(Lond.), F.R.C.S.(Eng.), F.I.C.S. Third edition. (Pp. 706+xvi; illustrated. Rs. 28.) Bombay: Popular Book Depot. 1960.

Facing Retirement. A Guide to the Middle Aged and Elderly. By a Country Doctor, M.A., M.D. (Pp. 127. 12s. 6d.) London: George Allen and Unwin, Ltd. 1960.

Clinical Anatomy. A Revision and Applied Anatomy for Clinical Students. By Harold Ellis, M.A., M.Ch.(Oxon.), F.R.C.S. (Pp. 369+xvi; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

Discussions on Child Development. A Consideration of the Biological, Psychological, and Cultural Approaches to the Understanding of Human Development and Behaviour. Edited by J. M. Tanner, M.D., D.Sc., D.P.M., and Bärbel Inhelder. Volume 4. (Pp. 186+xiii. 30s.) London: Tavistock Publications. 1960.

Clinical Pharmacology. By D. R. Laurence, M.D., M.R.C.P., and R. Moulton, M.B. (Pp. 490+viii. 32s.) London: J. and A. Churchill, Ltd. 1960.

Dr. Ida. The Story of Dr. Ida Scudder of Vellore. By Dorothy Clarke Wilson. (Pp. 350; illustrated. 21s.) London: Hodder and Stoughton. 1960.

Self-organizing Systems. Proceedings of an Interdisciplinary Conference, May 5 and 6, 1959. Edited by Marshall C. Yovits and Scott Cameron. (Pp. 322+xi; illustrated. 60s.) New York, Oxford, London, Paris: Symposium Publications Division, Pergamon Press. 1960.

The Medical Annual. A Year Book of Treatment and Practitioners' Index. Edited by R. Bodley Scott, M.A., D.M., F.R.C.P., and R. Milnes Walker, M.S.(Lond.), F.R.C.S. 78th Year. (Pp. 572; illustrated. 42s.) Bristol: John Wright and Sons, Ltd. 1960.

Councils, Committees and Concern for the Old. A Study for the Provision, Extent and Co-ordination of Certain Services for Old People in the County of London. By Kathleen M. Slack. (Pp. 160. 7s. 6d.) Welwyn, Herts: The Codicote Press. 1960.

Einführung in die Physiologie des Menschen. By Hermann Rein. 13th and 14th editions edited by Dr. Max Schneider. (Pp. 765+xii; illustrated. DM. 59.60.) Berlin, Göttingen, Heidelberg: Springer-Verlag. 1960.

Hearing. A Handbook for Laymen. By Norton Canfield, M.D. (Pp. 176. 12s. 6d.) London: Eyre and Spottiswoode. 1960.

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SALARY CRISIS AT CAMBRIDGE

On December 2 and 3 Cambridge University will vote on recommendations made to it by the General Board in a way which many fear will lead to the decline and fall of the Cambridge Medical School. Everyone, both inside and outside Cambridge, would, it is hardly necessary to say, regard this as nothing short of a disaster. The crux of the controversy into which the academic body of Cambridge is now plunged is the higher salaries which the University Grants Committee considers should be paid to clinical staff, salaries which separate them off as a special group within an academic society of a collegiate university. Cambridge thus brings to a head the widespread dissatisfaction in British universities about the differentials existing between the clinical staff holding university appointments as compared with those working in other faculties and departments. These differentials are, of course, the result of the nationalization of the medical profession in 1948, as the acceptance of entry into the National Health Service in that year was dependent upon the payment offered to the various categories of medical practitioners taking part in it. For universities the governing factor was the scales laid down in the Consultant Spens Report. Whatever may be the views in different universities on distinction awards, it may be said here that this is a matter which does not worry Cambridge, if only for the reason that relatively few of its clinical officers appear to receive them. The policy of the British Medical Association as approved by the Representative Body in July, 1956, is that "medical men and women in whatever form of medical practice or service they are engaged should be remunerated as doctors." And the B.M.A. holds that this remuneration should not be determined by relation to that of others employed in the same sphere. In the light of this policy the Non-professorial Medical Teachers and Research Workers Group Committee of the B.M.A. earlier this month (see *Supplement* p. 216) expressed their dissatisfaction with the new academic salaries for clinical staff now proposed by the University Grants Committee as not being high enough—salaries which the General Board of Cambridge University dislike because they are *in excess* of those paid to corresponding university officers in other faculties and departments. There is in this situation the seed of a conflict that will produce unending bitterness and dissatisfaction to the detriment of all those who, from one standpoint or another, feel themselves aggrieved.

The General Board of Cambridge University has made a long report on stipends which contains an exhaustive analysis of the position in Cambridge to-day,[1] and a subsequent and shorter report[2] which is an addendum made on the basis of the detailed knowledge of the University Grants Committee's recommendations for clinical staff. The first report is perhaps one of the most important statements that has yet been made on the remuneration of university teachers, and if the first of the General Board's recommendations wins the day when the vote is taken on December 2 and 3 the repercussions will be felt far beyond the walls of this ancient university. In brief, the Board considers that there should be no differentiations of payment which will separate out as a specially privileged group those university officers who will have the advantage over their non-medical university colleagues by virtue of having clinical responsibility.

The revision of salaries in 1949 consequent upon the impact of the report of the Spens Committee on the remuneration of consultants introduced what the General Board[1] describes as "the three-class system of stipends." Cambridge, a historical note to its eleventh report states, "went as far as any university in the country and further than most in resisting the differentiation introduced by the University Grants Committee and (that) progressively since 1949 other universities have come to share the point of view held then by the majority in Cambridge." The Board now states that the concessions were made in 1949 because it was not thought to be in the general interests of the university that the whole of the supplementary Treasury grant should be rejected in order to preserve non-differentiation. The Board also recognized the fears of those who felt that refusal to compromise might impair recruitment to, and the prestige of, the medical departments. It seems that the Board now regrets the compromise of 1949, and states that it has since supported recommendations "about the grave damage to the morale of University staff that may result from the divisions created by the three-class system of stipends." The principle behind this is

[1] *Cambridge University Reporter*, November 3, 1960, Vol. XCI. No. 9. Price 6d.
[2] *Cambridge University Reporter*, November 9, 1960, Vol. XCI. No. 11. Price 6d.

well expressed in the following quotation from the Board's eleventh Report[1]:

> "Their own view is, as it has always been, that academic life should be a vocation, in which adequate provision should be made for its followers to sustain an appropriate standard of life, but without undue reference to levels of remuneration in other fields, and without detailed comparisons between one office and another based on the amount or nature of work, or the relative importance of work in different subjects, judged by its assumed value to the community or by any other criteria. The communal atmosphere which the Board think should prevail in a University is apt to be vitiated by marked differences in the scales of remuneration or other conditions of employment of officers of the same grade and seniority, in whatever subject. Despite the existing differences mentioned in paragraph 19 [among these, scales of stipend in clinical departments], and others less ponderable, the General Board are of the opinion that the University is still an essentially homogeneous society, that it is in the interests of the University to preserve that homogeneity as far as possible, and that any development that is likely seriously to impair it should be resisted."

In subsequent paragraphs the Board returns again to its conception—a conception that is fundamental—of a university. "It is the maintenance of the unity of an academic profession, a University teaching profession, representing a common vocation, a common status, and a common interest." Arguments in favour of differentials the Board sees as a matter of expediency, and considers the real alternatives are that clinical staff should as a matter of principle have no differentials, or, alternatively, substantial differentials that will enable the university to compete with the National Health Service and other universities in the recruitment of staff.

So far as the centrepiece of the controversy is concerned—the payment of clinical staff—the first of the recommendations to be voted on is as follows:

> "That scales of University stipend be the same for all officers in the same grade whatever the Faculty or Department to which they are attached."

The second is:

> "That, even if Recommendation I be rejected, scales of University stipend, nevertheless, be the same for all officers in each grade in pre-clinical Departments as they are for officers in the corresponding grade in non-medical Faculties and Departments."

In its second and shorter report[2] the Board sets out three schemes for the remuneration of clinical staff. Scheme A will follow upon the acceptance of the first recommendation that there will be no differentials. If the first recommendation is rejected, a vote will be taken on the General Board's Scheme C, which introduces the differentials for clinical staff recently recommended by the University Grants Committee (see *Supplement* p. 216). If both these recommendations are rejected, then a vote will be taken on Scheme D, which proposes the continuation of the present differentials.

We have attempted to pick out from a long and complicated report, complicated because of a number of factors peculiar to a collegiate university and many of them peculiar to Cambridge itself, the essential facts so far as they relate to the payment of clinical staff. In the stormy debate that preceded the introduction of the N.H.S. few perhaps foresaw the impact of the Spens consultant proposals on the remuneration of university staff. So far as we understand the tenor of the General Board's report, there does not seem to be recognition of the likelihood that academic salaries generally have improved *because of* the payment of hospital staff in terms of the Spens recommendations. And now comes the revision—admittedly not satisfactory—by the University Grants Committee consequent upon the recommendations of the Royal Commission on the Remuneration of Doctors and Dentists in the National Health Service.

Most universities, and all who wish to preserve the university ideal in a commercial community, will sympathize with the general thesis sustained by Cambridge University's General Board. This country's struggle for survival in a harshly competitive world will depend first and foremost upon the quality of its brains and the opportunity afforded their owners to live a life of creative activity free from the dissatisfactions and embitterments caused by financial divisions within the university society produced by the strength or weakness of the bargaining powers of different groups. Nevertheless we hope that the vote on December 2 and 3 will be against Recommendation I; and not just because this falls into line with the policy of the British Medical Association on the payment of doctors. In answer to a question in May this year the Chancellor of the Exchequer said: "I am satisfied that a revision of the salaries of academic staff at the Universities is now necessary if regard is to be had both to salary increases in comparable professions and to the need to retain and recruit staff of adequate calibre during the forthcoming period of great expansion in the Universities. . . . Some Universities, however, are having particular difficulty in attracting or retaining academic staff of adequate calibre in a number of fields—in certain of the Arts subjects as well as in the Pure and Applied Sciences—where competition is peculiarly intense." Surely what Cambridge should do should be to accept the present proposals of the University Grants Committee for the remuneration of

clinical staff—accept, in other words, this differential against its officers in other faculties and departments—and then forthwith persist, with all the cogency and force of argument displayed in the eleventh report of its General Board, in bringing up the remuneration of the rest of the academic society to the level of its clinical officers. It would be nothing short of a tragedy if a vote in favour of Recommendation I were to threaten the existence of one of the greatest medical schools in this country, let alone, in the first instance, deprive a generation of students of the quality of teaching and inspiration that has been the hallmark of a university which at least has never been known as the home of lost causes. We hope that those who vote on December 2 and 3 will keep in the front of their minds the fact that doctors agreed to go into the Health Service in 1948 on certain terms and conditions, and that the acceptance of these terms and conditions brought to the front the completely inadequate remuneration of academic staff in the universities of Britain. What success the medical profession may have achieved in adjusting the payment of its members in relation to the conditions of to-day should be looked upon as a weapon to be used by the academic society to improve its own lot rather than to attempt to hold back a particular section of it.

FOETAL IRRADIATION AND LEUKAEMIA

The identification of the cause or causes of leukaemia in man remains obscure. It is still to be determined whether this is a single disease with protean forms or a number of different diseases having a common feature of dyshaemopoiesis. No frontal attack on the problem by the experimental approach is ethically acceptable. Therefore the conventional tactics of a double outflanking movement have been adopted—on the one hand the investigation of the leukaemias of experimental animals by all the available means of the laboratory, and on the other hand the collection and evaluation of human statistics.

From the laboratory we learn that the genetic background is a relevant factor, and, by selective breeding, lines of animals with a high natural incidence of one or other form of leukaemia can be developed. Moreover, in lines with a low spontaneous incidence, leukaemia can be induced by physical means—for example, *x*-irradiation—by chemical means, such as exogenous carcinogens and alteration of the endogenous hormonal balance, and by the biological means of certain viruses. Opinion is hardening to the view of L. Gross[1] that all such leukaemias in fowls and mice are due to an action of viruses which can be enhanced or suppressed under various conditions.

The human condition most comparable with the "leukaemias" of mice and fowl is acute leukaemia, but so far no viral agents have been found to account for the varieties of different cellular type.[2] Acute leukaemia of the newborn is rare, but individual case reports appear intermittently. Acute leukaemia of young children, often lymphoblastic, has according to available statistics increased in incidence during the last generation but less than in the aged.[3] Much of the increase may be due to better recognition.[4] Much may be due to the survival under modern conditions of those children who formerly might have died in infancy from specific infections which are now controlled by immunization or antibiotics.[5] Notable among such children are mongols. The association of leukaemia with mongolism is now well known, and mongolism is associated with the presence of a chromosome additional to the normal diploid complement.[6] The normal balance of genes is thereby disturbed. Evidence, only some of which is published,[7 8 9] is accumulating to show that acute leukaemia is also sometimes associated with visible abnormalities of the chromosomes, a phenomenon already observed in leukaemic mice[10]; and this, too, would lead to genetic unbalance. Chromosomal abnormalities of this type are regularly produced by exposure to *x* rays and similar radiations.[11] *In vitro*, cells carrying such abnormal complements are usually not able satisfactorily to reproduce by mitosis.[12] *In vivo*, however, they may remain as cell nests, and under conditions of abnormal environment some may be able to divide and release themselves from the normal mechanisms of control.

Whatever may be the correct explanation of observations accepted as facts, there are other observations which still require validation. From the practical aspect the most important was that of Alice Stewart and her colleagues.[13] From a retrospective statistical survey of cases of malignancy in childhood, they derived an association of malignancy with *x*-irradiation during foetal life, suggesting that such

[1] Gross, L., *Acta haemat. (Basel)*, 1960, **23**, 259; and *Brit. med. J.*, 1958, **2**, 1.
[2] Braunsteiner, H., Fellinger, K., and Pakesch, F., *Blood*, 1960, **15**, 476.
[3] Brown, W. M. C., and Doll, R., *Brit. med. J.*, 1959, **1**, 1063.
[4] Wood, E. E., ibid., 1960 **1**, 1760.
[5] Stewart, A., *Lancet*, 1960, **2**, 853.
[6] Lejeune, J., Gautier, M., and Turpin, R., *C.R. Acad. Sci. (Paris)*, 1959, **248**, 1721.
[7] Ford, C. E., Jacobs, P. A., and Lajtha, L. G., *Nature (Lond.)*, 1958, **181**, 1565.
[8] Baikie, A. G., Brown, W. M. C., Jacobs, P. A., and Milne, J. S., *Lancet*, 1959, **2**, 425.
[9] Nowell, P. C., and Hungerford, D. A., *J. nat. Cancer Inst.*, 1960, **25**, 85.
[10] Ford, C. E., and Mole, R. H., in *Progress in Nuclear Energy Series VI. Biological Sciences*, Volume 2, 1959, p. 11. London.
[11] Lea, D. E., *Actions of Radiations on Living Cells*, 2nd ed., 1955, Chapter 6, Cambridge University Press.
[12] Puck, T. T., *Proc. nat. Acad. Sci.*, 1958, **44**, 772.
[13] Stewart, A., Webb, J., and Hewitt, D., *Brit. med. J.*, 1958, **1**, 1495.
[14] Ministry of Health. *Radiological Hazards to Patients. Interim Report* 1959, H.M.S.O. London.

irradiated children had twice the normal chance of dying from malignancy before the age of 10. In the opening pages of the *Journal* this week Dr. W. M. Court Brown, Dr. R. Doll, and Professor A. Bradford Hill review what confirmation or lack of it there has been from other surveys and give their own statistics to date of a prospective survey of children who had been exposed while still *in utero* to *x* rays applied for diagnostic purposes. There were 9 deaths from leukaemia before the age of 14 instead of the expected 10.5 from the group of 40,000-odd children in the survey. Mr. T. L. T. Lewis also reports the results of an investigation into this problem (p. 1551), obtaining a negative result from an analysis of records from Queen Charlotte's Hospital, London.

These figures illustrate the difficulty of this type of statistical investigation. The death-rates from leukaemia even in a period of 10 years or so are small, so that differences between the control and investigated groups must in absolute numbers be small, and significance rests on the relativity. Retrospective surveys are suspect because they depend on past history, and human memory is fallible. Prospective surveys may suffer from the failure to identify some real consequences of the act investigated; but in general more confidence is engendered by the prospective survey.

In the present context the reader will not find scientific disproof of either hypothesis. It is possible here only to attempt a judicious opinion. The results of Court Brown and his colleagues suggest that, if leukaemia is induced in children by diagnostic irradiation as practised in the respective hospitals at the revelant time, it was too infrequent to be detectable by an investigation of manageable size. From the much larger numbers of cases of malignancy in childhood which Stewart and her colleagues were able to select, we must conclude that, if diagnostic irradiation had the carcinogenic effect their statistics indicated, the capacity of *x* rays for the production of leukaemia was 10 times or more greater in the foetus than at any other age.

What the clinician needs to know is: Will the use of diagnostic *x* rays on the abdomen of the pregnant women or the withholding of them lead to the greater human suffering? There seems to have been no published appreciation of this problem. The Committee on Radiological Hazards to Patients[14] has evaluated the situation for mass miniature radiography and concluded that the benefits of early identification of curable pulmonary disease far outweigh the disadvantages of the calculated numbers of cases of induced leukaemia. The answer for obstetric radiology rests on the provision of quantitative data by the obstetrician of how much the recent reduction in maternal and foetal morbidity and mortality has been attributable to the information derived from *x* rays. Against this can be set the possible numbers of malformations and neoplasms induced by the radiation. On radiobiological grounds it seems likely that the hazard is preponderantly from radiation given to the embryo in the first trimester. There are thus sound reasons for advising delay of diagnostic irradiation when possible.

CARDIAC MASSAGE WITHOUT THORACOTOMY

Special facilities for emergency resuscitation by intrathoracic cardiac massage are now accepted as an essential hospital service in connexion with cardiac surgery. The provision of this service, however, has itself raised new questions about the indications for cardiac resuscitation. All are agreed that when a patient develops ventricular fibrillation or cardiac standstill during an operation or induction of anaesthesia, no effort should be spared in attempting to get the heart beating again within the shortest possible time to prevent the irreversible damage that anoxia may cause. This necessitates immediate intrathoracic cardiac massage and mouth-to-mouth respiration until the apparatus for giving oxygen through an endotracheal tube and for defibrillation is available. Outside the operating theatre, however, when "death" occurs suddenly from ventricular standstill or fibrillation, there is less general agreement about the correct course of action: this will depend on the presence or absence of a known cardiac lesion and its nature and prognosis, the age of the patient and his general health, and finally on the likelihood of success of resuscitation in the prevailing circumstances. There are now a number of reports of successful resuscitation by intrathoracic cardiac massage of medical patients who have had sudden cardiac arrest from cardiac infarction[1,2] or even after an electric shock.[3] On the other hand, there have been other cases in which attempted resuscitation with all its inevitable disturbances in the ward or elsewhere has proved unsuccessful, and in which there has been little real hope of success from the beginning because of the gravity of the disease from which the patient was suffering.

A new method of performing cardiac massage without thoracotomy has been reported by W. B. Kouwenhoven, J. R. Jude, and G. G. Knickerbocker,[4]

[1] Beck, C. S., Weckesser, E. C., and Barry, F. M., *J. Amer. med. Ass.*, 1956, 161, 434.
[2] Walton, R. S., *Brit. med. J.*, 1960, 1, 155.
[3] Halpern, R., and Weber, A. O., quoted by Beck, C. S., and Leighninger, D. S., *J. Amer. med. Ass.*, 1960, 174, 133.
[4] Kouwenhoven, W. B., Jude, J. R., and Knickerbocker, G. G., ibid., 1960, 173, 1064.
[5] Zoll P. M., Linenthal, A. J., Gibson, W., Paul, M. H., and Norman, L. R., *New Engl. J. Med.*, 1956, 254, 727.
[6] Kouwenhoven, W. B., Milnor, W. R., Knickerbocker, G. G., and Chesnut, W. R., *Surgery*, 1957, 42, 550.

of the Johns Hopkins University School of Medicine, and if experience proves this effective it may well become the method of choice for medical, as opposed to surgical and anaesthetic, emergencies. They performed experiments on 100 dogs, testing various methods of moving the blood by massaging the intact chest, and claim to have developed a safe and effective method of massaging the heart without opening the thorax. By intermittent manual pressure on the anterior chest wall they were able to produce a systolic pressure in the femoral artery of 100 mm. Hg, with a mean of 50 mm. Hg, in dogs with ventricular fibrillation. After half an hour, during which closed-chest cardiac massage was continued without interruption, normal sinus rhythm returned immediately in response to a shock from an external defibrillator.

Kouwenhoven and his colleagues also report the successful resuscitation of 20 patients by the same technique of closed-chest cardiac massage: 14 are alive and show no signs of damage to the central nervous system. Three of the 20 patients were in ventricular fibrillation and were successfully defibrillated by an external defibrillator.[5,6] The duration of cardiac massage varied from one to 65 minutes. In seven cases the progress of the patient during treatment was monitored by electrocardiographic or blood-pressure recordings. Of the five cases described in detail, four became pulseless during anaesthesia or operation, and one after a cardiac infarction.

The principle of their method of closed-chest cardiac massage is that pressure on the sternum compresses the heart between it and the spine, thus forcing blood out of the heart. Relaxation of pressure allows the heart to fill. The thoracic cage is sufficiently mobile in unconscious and anaesthetized patients to permit this manœuvre. It is carried out by applying manual pressure on the sternum about 60 times a minute, depressing it 3 to 4 cm. towards the vertebral column.

Further experience of the efficacy of closed-chest cardiac massage is required before a final assessment can be made of its usefulness. Its simplicity and safety, its applicability at any time and place, not necessarily in a hospital, and the avoidance of thoracotomy are valuable features, and it is to be hoped that it may prove an important addition to the present techniques of cardiac resuscitation.

GLUCOSE TOLERANCE CURVE IN HIDRADENITIS SUPPURATIVA

In man the apocrine sweat glands are vestigial and lack any useful physiological function except in certain areas of the body, where they have become modified and specialized as the ceruminous glands of the external ear canal, or as Moll's glands of the eyelid, or, most important of all, the mammary glands. Apocrine sweat provides an excellent medium for bacterial growth, and it is perhaps surprising that clinical infection of these glands is comparatively rare. Hidradenitis suppurativa is a severe chronic infection of the apocrine sweat glands presenting a notoriously difficult therapeutic problem. It usually affects the axillae and groins, but it is also seen in the areolae and perianal skin. It produces not only chronic boggy granulomatous masses and much scarring locally but also considerable systemic upset. Even prolonged systemic administration of antibiotics may fail, and extensive plastic surgery may be the only effective treatment in severe cases.

R. M. B. MacKenna and H. Lehmann[1] recently studied this condition in seven female patients aged 19–52. During their investigation they found that five had "flat" glucose tolerance curves, one had a "diabetic" response, and one a "lag" or "steeple" type of curve. Because "flat" glucose-tolerance curves have been observed in patients suffering from malnutrition and apparently associated skin lesions, which improved dramatically on an adequate diet reinforced by an excess of riboflavin, Mackenna and Lehmann gave six of their patients 3 mg. of riboflavin thrice daily. The lesions disappeared slowly but satisfactorily, and after several months the riboflavin could in some, but not all, cases be stopped "without relapse of the malady." However, even after recovery of the skin condition the type of blood-sugar tolerance curve remained unaltered. One of these patients was further investigated, and it was found that the flat curve was not due either to hyper-insulinism or to undue sensitivity to insulin. She also showed impaired ability of absorbing vitamin A. These findings suggest that for some reason utilization of glucose by the intestinal mucosa is deficient in a high proportion of these patients and that there may be other defects of absorption or metabolism. In idiopathic steatorrhoea the flat glucose-tolerance curves are associated with delayed absorption from the small intestine, which is attributed to excessive secretion of mucus and diminished intestinal motility.[2–4] MacKenna and Lehmann do not mention whether their patients showed evidence of idiopathic steatorrhoea or of thyroid or suprarenal cortical insufficiency, but obviously there was no causal relationship between the flat glucose-tolerance curve, which remained unchanged during the period of observation, and the skin condition, which improved so strikingly.

The presence of several apparently unrelated abnormalities suggests the search for a common factor. Hormonal imbalance has long been regarded as of greater importance in hidradenitis suppurativa than the infecting organism, and high doses of testosterone have proved beneficial in some cases. MacKenna and Lehmann's work suggests that the mechanism of this condition may be more complex than previously suspected. Metabolic disorders, like diabetes mellitus, may profoundly affect many tissues and organs yet often escape clinical detection until they affect the skin, thus producing overt disease. Much fundamental knowledge may still be gained from studying more closely some common chronic disorders apparently confined to the skin. They

[1] MacKenna, R. M. B., and Lehmann, H., *Brit. J. Derm.*, 1960, **72**, 142.
[2] Groen, J., *New Engl. J. Med.*, 1958, **258**, 247.
[3] Frazer, A. C., French, J. M., Thomas, G., and Thompson, M. D., *Clin. Sci.*, 1952, **11**, 141.
[4] Gaddie, R., Thomas, G., Smith, N., and French, J. M., *Quart. J. Med.*, 1957, New Series **26**, 121.

may well be like the protruding portion of an iceberg, and their investigation may lead to a better understanding of processes affecting organs less accessible to observation and experiment than the skin.

OLD AND ILL IN LONDON

The London Local Medical Committee has recently been trying to find out if there was any substantial number of old people in London who were not receiving the treatment they needed. According to a report[1] prepared by the committee not many patients with treatable medical disabilities remained untreated. The committee was well satisfied with the quality of the local authority services and, in most areas, with their quantity, though at week-ends it was sometimes difficult to obtain home helps and other personal services in an emergency.

Many of the improvements in the services available to the old and infirm stem from the work of voluntary organizations. The recently published annual report[2] of the National Old People's Welfare Council shows what is still accomplished by voluntary effort. So far as hospital treatment is concerned, the King Edward's Hospital Fund for London administers an admirable "hospital personal aid service for the elderly," under the chairmanship of Sir Zachary Cope. This has now been in existence for ten years and its work is reviewed in a recent report.[3] This service undertakes to visit (but only at the request of hospitals) elderly people awaiting admission but who are not ill enough to need immediate treatment in an acute ward, and to provide a centre where hospitals and doctors can obtain assistance in dealing with the problems of the elderly and chronically ill.

When this was started it was soon apparent that hospitals had little knowledge of the needs of many of the elderly patients on their waiting-lists. As a result of the first investigation of 400 patients on the waiting-lists of five hospital groups, it was found that a quarter of them had died or had been admitted and that a large number of the others either refused to go to hospital or were suitable for some other form of care. As a result, other provision was made for 127 of these patients and their names were consequently removed from the waiting-lists. In 1959, 2,420 patients were visited at the request of hospitals, and 45% were taken off the waiting-lists. For 558 patients (23%) other arrangements were made with the approval of their doctors. It is now the experience of the King's Fund that more elderly patients are being admitted to hospital quickly and fewer wait for a long time. In 1952 23% waited over two months, but this had fallen to just over 1% in 1959. By 1955 2,164 patients had been visited by the service and admitted to hospital, and at the end of that year 48% had died, 36% had been discharged, and 16% were still in hospital. By 1959 the total had gone up to 5,915, and the corresponding figures were 50%, 44%, and 6%. The fall in the percentage of patients remaining in hospital is accounted for not by deaths but by the greater proportion discharged.

An important conclusion which the King's Fund has come to as a result of this work is that "there is still much to be done to achieve what should be the first aim of hospitals—namely, the accurate diagnosis and treatment of patients of no matter what age." New buildings may be needed at many hospitals, but better use could often be made of existing accommodation.

[1] See *Supplement, Brit. med. J.*, 1960, **2**, 128.
[2] The National Old People's Welfare Council, *Annual Report for the Year Ending 31st March, 1960*, National Council of Social Service, 26 Bedford Square, London W.C.1. Price 1s. 6d. net.
[3] King Edward's Hospital Fund for London, *Hospital Personal Aid Service for the Elderly, Report to 31st December, 1959*. The office of the service is at New Cross General Hospital, London S.E.14. Tel. New Cross 3635.

BIOLOGY AND ENGINEERING

The Biological Engineering Society was created earlier this year and has recently had its first scientific meeting.[1] The society grew out of the British Section of the International Federation for Medical Electronics. It had become increasingly apparent to members of that body, and to other workers in parallel fields, that, though there was an undoubted need for greater understanding between medical men and electronic engineers for the solution of instrumentation problems, this was only one aspect of a much broader picture. There are many areas in which the fields of biology and engineering overlap. The provision of suitable materials for grafts and implants, the design of powered limb prostheses, the large-scale production of enzymes and hormones, the mechanization of laboratory techniques, the construction of artificial organs, and the applications of computers are examples.

Progress in these directions is sometimes impeded because the engineer and the biologist do not talk the same language and do not fully understand each other's problems. The aim of the new society is to provide a meeting-ground on which people working in the engineering sciences can forgather with medical men and biologists. The society will hold meetings three or four times a year, at which papers will be read and demonstrations given. The meetings will take place in various cities in Great Britain, sometimes in hospitals and sometimes in research establishments, laboratories, and plants devoted to engineering or to biological sciences. It is appropriate that the first meeting should have been held at the National Institute for Medical Research, a place where there is already much fruitful interaction between biologists and engineers.

Another aim of the Society is the establishment of a central store of information about various aspects of biological engineering, so that workers confronted with a problem may be put in touch with others who might help to solve it, or be given a digest of recent literature on the subject. There are also plans to produce a new journal devoted to biological engineering, with which the Society will be associated. The president of the Biological Engineering Society is Dr. Ronald Woolmer, professor of anaesthesia in the Royal College of Surgeons; and the secretary is Dr. A. Nightingale, Physics Laboratory, St. Thomas's Hospital, London S.E.1.

[1] *Brit. med. J.*, 1960, 2, 1448.

Clinicopathological Conference

A CASE OF ATRIAL SEPTAL DEFECT

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is an unusual case of atrial septal defect, in which the radiological features were especially puzzling. The patient was treated at Hammersmith Hospital (Case No. 129,659; P.M. No. 8,754).

Clinical History

Dr. J. F. GOODWIN: The patient was a woman aged 52 years at the time of her death. At the age of 11 years congenital heart disease was diagnosed, and she had been dyspnoeic on exertion since childhood. Despite this she had lived an active life and had managed a normal pregnancy. In 1946 she developed painful swelling of the interphalangeal joints of the hands and of the shoulders, which caused disability. By 1948 her intolerance of effort had increased, and she was breathless on slight or moderate exertion. She developed bronchitis in the winter, but had no pain in the chest or haemoptysis.

EXAMINATION AND INVESTIGATIONS

On examination in 1951, when aged 44, she was found to be a sallow, thin, woman with typical rheumatoid arthritis. The cardiovascular system revealed normal arterial and venous pulses, but the cardiac impulse was diffuse and lifted the sternum, indicating an enlarged and dilated right ventricle. The left ventricle was impalpable. The second heart sound was widely duplicated, and fixed. There was a short ejection-murmur of medium intensity in the pulmonary area, but no diastolic murmurs were heard. The blood-pressure was 115/80 mm. Hg. There was no cyanosis or clubbing, and the remainder of the physical examination was normal except for scattered rhonchi at the bases of the lungs. *Blood.*—Hb 100%; W.B.C. 12,000; E.S.R. 30 mm./1 hr.; urea 21 mg./100 ml.; liver-function tests normal. *Urine.*—Normal.

Cardiography.—Sinus rhythm with right bundle-branch block, right axis deviation, and right ventricular hypertrophy (Fig. 1).

Radiography.—There was right atrial and right ventricular enlargement. The pulmonary artery and its main branches were greatly distended. The aorta was small. The left atrium was not enlarged. The pulmonary blood flow was increased. No intracardiac calcification was noted. Radiographs of the hand showed chronic arthritis of rheumatoid type.

Cardiac Catheterization (25/9/51).—There was a left-to-right shunt at atrial level, the pulmonary:systemic flow ratio being 2.3:1. No anomalous pulmonary veins were encountered. The mean pulmonary-artery pressure was 26 mm. Hg, the pulmonary vascular resistance being within normal limits. Arterial oxygen-saturation was 88%.

Diagnoses of ostium secundum type of atrial septal defect and of rheumatoid arthritis were made.

PROGRESS

The patient did not attend hospital regularly, but apparently remained reasonably well until 1955, when her dyspnoea increased, although she was mainly limited by her arthritis. The cardiovascular signs (see Figs. 2a and 2b) were unchanged. Operation to close the atrial septal defect was now considered. The patient was not anxious for the operation, being mainly disabled by her rheumatoid arthritis, and in view of the adverse features of her age and the size of her heart the matter was not pressed.

SECOND ADMISSION

In September, 1956, she was admitted to hospital for the second time because of increasing dyspnoea and bronchitis. The jugular venous pressure was now 4 cm. above the sternal angle. Atrial fibrillation was noted for the first time. Dyspnoea improved, and the venous pressure fell to normal on cardiac therapy. Radiological examination of the chest showed narrowing of the segmental arteries at the bases, but not the apices, of the lungs, and doubtful enlargement of the left atrium (Figs. 3a and 3b).

THIRD ADMISSION

One year later she was admitted for treatment of her rheumatoid arthritis with serial plasters. At this time a tricuspid diastolic murmur was noted for the first time. Her condition remained satisfactory until March, 1959, when she developed a cough with yellow sputum, fever, and severe dyspnoea.

FOURTH ADMISSION

On admission to hospital she was gravely ill, with cyanosis and severe dyspnoea. The jugular venous pressure was 3 cm. above the sternal angle. There were sticky rales throughout the lungs, respiration was rapid and laboured, and the air-entry poor over the lower lobes. Her temperature was 99–100°F. (37.2–

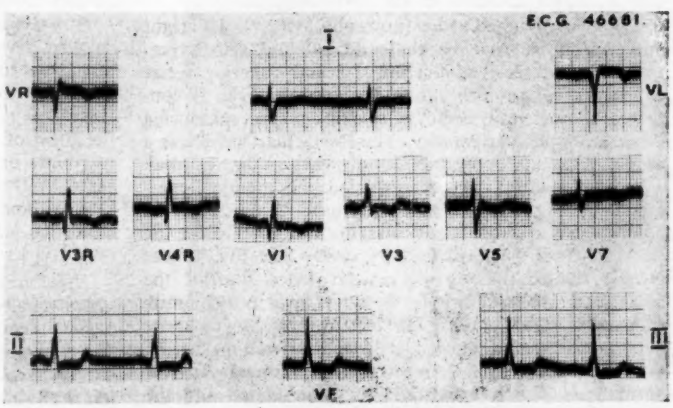


FIG. 1.—Cardiogram in 1951, showing right bundle-branch block, right ventricular hypertrophy, and right axis deviation. Sinus rhythm. P waves normal. PR interval 0.2 sec.

37.8° C.). There was no oedema. *Blood.*—W.B.C. 15,000 (85% polymorphs); E.S.R. 15 mm./1 hr. *Electrolytes.*—HCO_3 40 mEq/litre; Na 133, K 3.9, Cl 77 mEq/litre; urea 28, rising to 70 mg./100 ml. *Urine.*—Reaction acid; heavy cloud of albumin. *Sputum.*—Pus cells; *H. influenzae* and *Strep. viridans.* Radiological examination of the chest showed patchy consolidation and collapse of both lower lobes.

A diagnosis of acute bronchitis and bronchopneumonia was made, and she was treated with moistened oxygen and isoprenaline inhalations, intravenous aminophylline, digitalis, diuretics (with potassium chloride supplements), and chest physiotherapy. The oxygen did not improve her cyanosis, and, although the sputum became clear on March 15, she deteriorated, becoming drowsy and developing twitching movements. Carbon-dioxide narcosis was considered probable, but tracheostomy was decided against as she was ventilating well, the sputum was thin, and the larger airways apparently clear. A single-breath test with the mass spectrometer did not suggest a high carbon-dioxide tension, and her high serum bicarbonate was thought possibly to be due to a metabolic alkalosis, the low chloride and sodium levels being the result of diuretic treatment in a patient severely ill from pneumonia. The acidity of the urine supported this view. Her mental state was thought to be due to a low cardiac output, if not to carbon-dioxide retention. She died suddenly on March 17, 1959.

Clinical Diagnosis

(1) Large ostium-secundum-type atrial septal defect.
(2) Rheumatoid arthritis.
(3) Bronchopneumonia.
(4) Heart failure.
(5) ? Respiratory acidosis due to pulmonary failure.
(6) ? Metabolic alkalosis.

Post-mortem Findings

Dr. MONICA BISHOP: The post-mortem examination was performed 12 hours after death. The body was that of a moderately well nourished, middle-aged woman with marked rheumatoid deformity of the hands, ulnar deviation, and thickening around the knee and wrist joints. No palpable nodules of rheumatoid type. None of the external stigmata of Marfan's syndrome. No generalized oedema or jaundice. 50 ml. of straw-coloured fluid was present in both of the pleural cavities and a similar quantity in the abdominal cavity.

The *heart* weighed 650 g. (normally 311 g.*). The right atrium (Fig. 4) was markedly dilated and also hypertrophied and received the inferior and superior venae cavae normally. The *interatrial septum* (Fig. 5) contained a large ovoid defect of secundum type, measuring 4 cm. at its widest diameter. The Eustachian valve was a much thicker and more substantial structure than normal. The right ventricle was also dilated and greatly hypertrophied, measuring 7 mm. (normally 3 mm.) at the conus, 5 mm. at the acute margin, and 10 mm. at the posterior wall. The *pulmonary artery* (see Fig. 4) was grossly dilated, having a diameter twice that of the aorta and a circumference at valve level of 110 mm. (normally 78–85 mm.). The left atrium showed more hypertrophy than dilatation, the posterior wall measuring 4 mm. in thickness. It received the pulmonary valves normally. The left ventricle was not dilated and the wall measured 15 mm. The atrio-ventricular *valves* were reduced in size. Tricuspid valve 105 mm. (normally 110–130 mm.), mitral valve 75 mm. (normally 90–110 mm.). The commissures and bases of these valves were normal, the narrowing being achieved in each case by thickening and sclerosis of the free margins of the leaflets, particularly the anterior ones, and scarring, shrinking, and thickening of the chordae to them (Fig. 6). Microscopically, myocardial lesions (Fig. 7) were present, taking the form of loose fibrocellular aggregates of recent origin. The cellular element was mainly lymphocytes and histiocytes with a few polymorphs. These were especially prominent in the right ventricle and right atrium. The right atrium showed also considerable interstitial fibrosis and scattered cellular infiltration, especially in the region of the sino-auricular node, where the presence of iron-filled macrophages was another indication of damage. In the ventricles there were also a few perivascular scars which may have been related to the presence of atheroma in the main coronaries. None of these lesions was typical of old or recent rheumatic infection.

The lower end of the *trachea* and the main *bronchi* were reddened and contained thick, purulent secretion, especially in the lower portions of the lungs. The external surface over both lung bases showed some loss of sheen, and there were light adhesions to the chest wall and between the lobes. Both lungs were overweight, the right weighing 760 g. and the left 680 g. (normally 400 g. and 320 g.), and the lower lobes in particular had the knobbly consistence of bronchopneumonia together with some pulmonary oedema. Arteriograms (see Figs. 10 and 11) were performed, and showed that the dilatation of the main *pulmonary artery* was continued along the main branches of the pulmonary arteries so that the larger elastic arteries all appeared dilated. In the lower zones of each lobe of the lung, however, particularly in the lower lobes, there appeared to be significant narrowing of the smaller branches. The peripheral and background filling of the smaller muscular arteries was not much reduced compared with that of a normal control, implying that there was no very significant degree of pulmonary hypertension superimposed upon these changes. The histology bore out this appearance, confirming the generalized nature of the dilatation of the elastic arteries and the presence in the upper zone (Fig. 8) of slight hypertrophy of the muscular arteries without obstruction of the lumen, but in the lower zones (Fig. 9) the lumen was severely narrowed and the muscular wall apparently much thicker. Evidence of acute bronchitis was found in most areas, but the bronchopneumonia was most intense in the lower zones. The histology also confirmed that there was no evidence of back pressure in the lungs in the form of heart-failure cells, hypertrophy of the walls of veins, or widening and fibrosis of the interlobular septa. There was thrombus in many of the smaller arteries and veins, the histology of which suggested, from its lack of organization, that it had probably occurred as an immediate pre-terminal event.

The *liver* weighed 1,350 g. (normally 1,400 g.), and histologically showed some fatty change and moderate passive venous congestion. The *right kidney* weighed 192 g. and the left 210 g. Both had a slightly granular surface, and the right was slightly more scarred than the left and showed a minimal degree of renal damage of pyelonephritic type. The other organs were normal.

*In a woman of height 5 ft. 7 in. (1.7 m.).

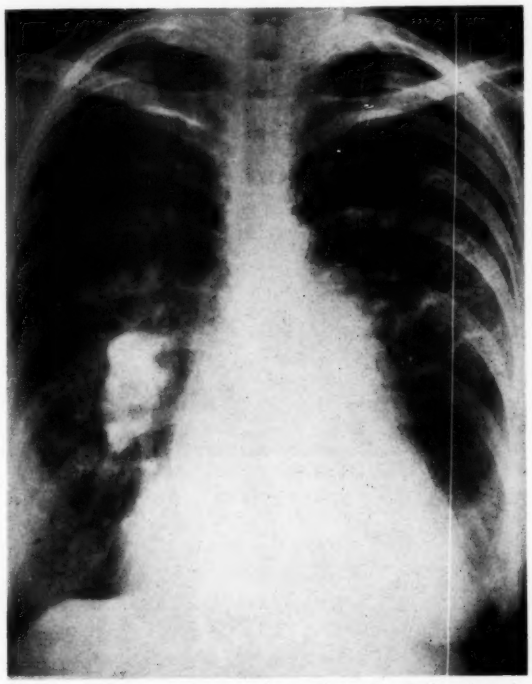


FIG. 2*a*.—Six-foot postero-anterior radiograph of the chest in 1955, showing enlargement of the right atrium and pulmonary arteries, with small aorta, and increased pulmonary blood flow.

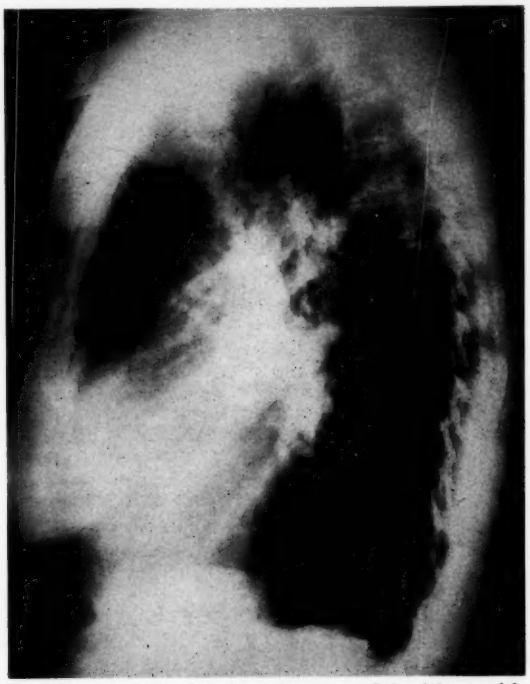


FIG. 2*b*.—Lateral film, showing enlargement of the right ventricle and main pulmonary artery.

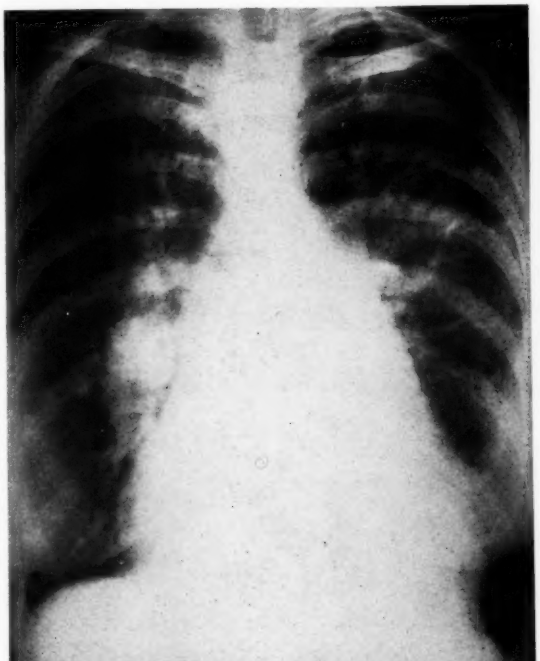


FIG. 3*a*.—Six-foot postero-anterior radiograph of the chest in 1956, showing prominent vascular markings in the upper zones of the lungs and deficient markings in the lower zones.

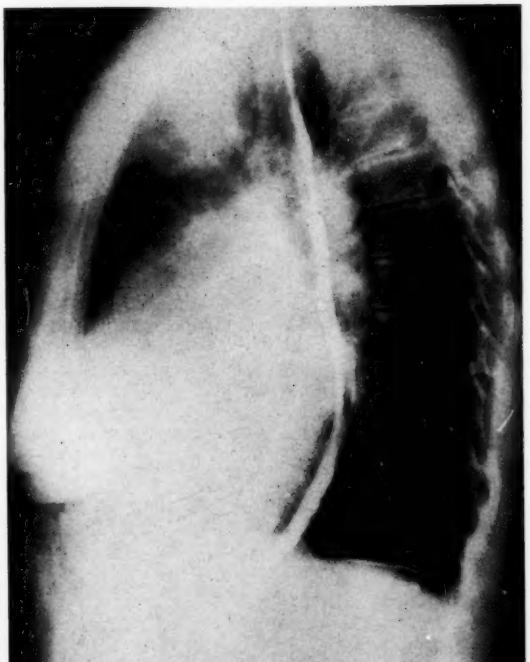


FIG. 3*b*.—Lateral film in 1958, showing minimal enlargement of the left atrium.

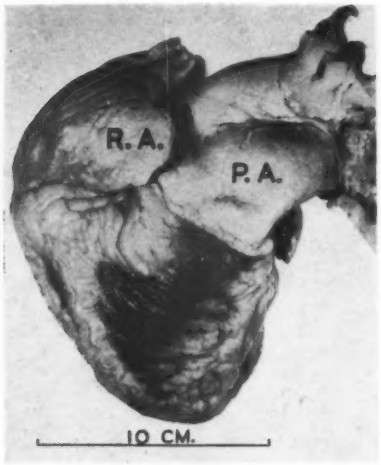


FIG. 4

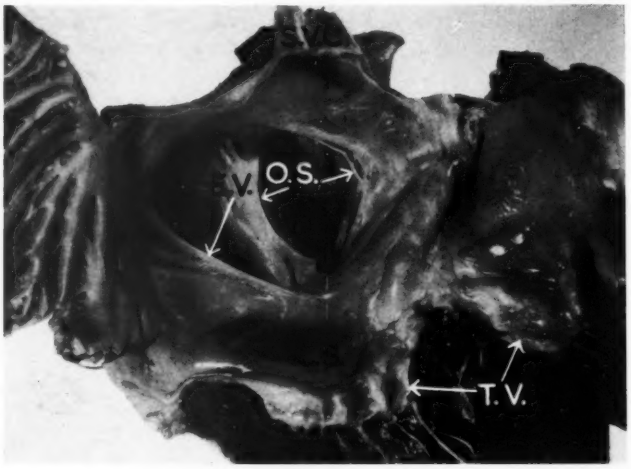


FIG. 5

FIG. 6

FIG. 7

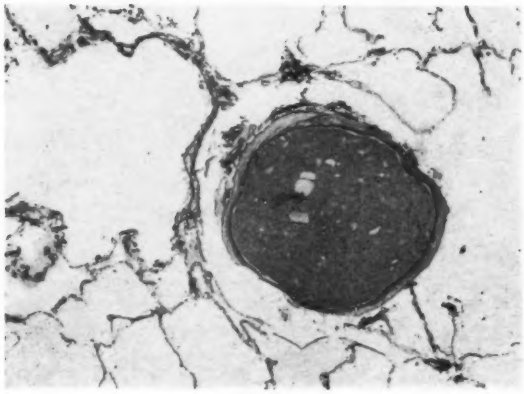


FIG. 8

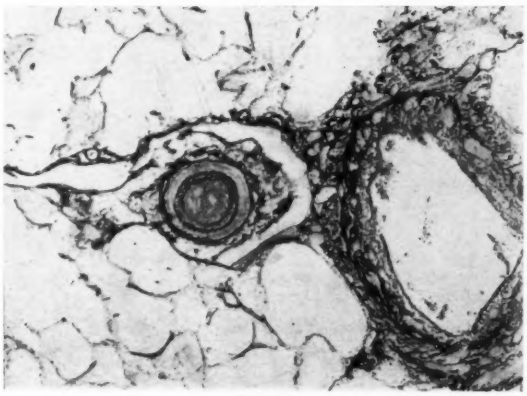


FIG. 9

Pathologist's Diagnosis

(1) *Heart.*—Congenital heart disease. Atrial septal defect of secundum type. Mitral and tricuspid valve sclerosis (? comprising Lutembacher's syndrome). Coronary atheromatosis. Mild myocarditis probably secondary to bronchopneumonia.

(2) *Lungs.*—Acute bronchitis. Severe bilateral basal bronchopneumonia. Pulmonary vascular pattern of atrial septal defect type, with differential narrowing of the type associated with mitral stenosis.

(3) *Kidneys.*—Mild chronic pyelonephritis.

(4) *Joints.*—Rheumatoid arthritis.

Discussion

Dr. GOODWIN: I should like to start the discussion on three counts: first, the nature of Lutembacher's syndrome; second, the course and treatment of atrial septal defect; and, third, the interesting terminal situation of this patient's respiratory failure about which I think Dr. Hugh-Jones would probably like to speak.

THE MITRAL STENOSIS

Dr. Bishop suggests we should call this Lutembacher's syndrome. I think the definition—if you wish to use the term—is mitral stenosis with atrial septal defect, with no comment as to how severe the stenosis is. It is worth considering how it can be diagnosed in life, for we failed completely to do so. When the atrial septum is patent, the haemodynamics and physical signs of mitral stenosis are modified because there is a safety valve, as it were, to the left atrium, while the mitral stenosis tends to perpetuate the left-to-right shunt, so that the left atrium does not enlarge to any extent, although the right atrium may do so.[1] The jugular venous pressure when tight mitral stenosis is associated with atrial septal defect tends to be persistently raised, and this is a sign which may make one suspect it. In this patient the jugular venous pressure was not persistently or notably raised, probably because the stenosis was not critical. The murmur of mitral stenosis is often very soft, or may be absent. We couldn't hear it in this patient. I think there are two reasons for this: one is that mitral valve flow is diminished in atrial septal defect, and I would here query Dr. Bishop's "wear-and-tear" story regarding the mitral valve, because it is rather starved in atrial septal defect, for a lot of the blood gets stolen by the right atrium owing to the left-to-right shunt. This tends to reduce mitral flow and thus diminish the murmur. The second reason is that the mitral diastolic murmur may be obscured by the tricuspid flow murmur, which may be heard to the left of the tricuspid area. The tricuspid murmur increases on inspiration, so if you hear a mid-diastolic murmur at the apex which increases on *expiration*, possibly with an opening snap, you may suspect mitral stenosis.

Other pointers to diagnosis are calcification of the mitral valve (which does not seem to be common in Lutembacher's syndrome), although I have seen it; and perhaps atrial fibrillation in young patients. I think the radiology of the lung vessels is particularly important. Selective narrowing of the segmental arteries to the lower lobes only strongly suggests a raised left atrial pressure due to mitral obstruction,[2] and I should have spotted this on the radiographs in 1956. Parkinson and Bedford[1] stressed the gross right atrial enlargement on *x*-ray examination, which we certainly didn't see here. Left atrial enlargement tends to be rather negligible, but in fact in this patient we did have one film which suggested slight enlargement of the left atrium, although others looked normal. Probably the only certain way to diagnose significant mitral stenosis in the presence of an atrial septal defect is to demonstrate a pressure gradient across the mitral valve by catheterization.

I am afraid we didn't even think of mitral stenosis at all, but of course I ought to have done because of the radiograph, and I should just like to show it to you again (see Fig. 3a). This is an example, I think, of being hoist with our own petard, or my own petard, because this selective narrowing of the basal arteries in mitral stenosis was described by Dr. Steiner, Professor Harrison, and myself a few years ago.[3] I think this radiological sign may enable one to suspect mitral stenosis in the presence of an atrial septal defect. The incidence of mitral stenosis with atrial septal defect is rather puzzling. It was found to occur in 4 of 10 necropsy cases described by Bedford *et al.*,[1] but subsequent series[4 5] have made the incidence between 4 and 6%.

PROGNOSIS OF THE SEPTAL DEFECT

It is worth saying just a word or two on the prognosis of atrial septal defect of the secundum type, in view of this patient's course and age at death. Without operation the average age of death in patients with large defects is 40–50 years, and I think this lady fitted in to the usual natural history of the disease fairly well. Patients with small defects, and a few with large ones, may live to extremes of age, and I know we have had some patients here who have lived into the seventies. The hazards of the disease are, of course, heart failure, due to the persistent left-to-right shunt; atrial fibrillation; and obliterative pulmonary hypertension, which is due probably to thrombo-embolism in the very

FIG. 4.—Anterior view of heart and great vessels, showing dilatation of the right atrium (R.A.) and pulmonary artery (P.A.).

FIG. 5.—Right atrium showing large septal defect. The arrows define the ostium secundum defect (O.S.). The Eustachian valve (E.V.) is unusually prominent. S.V.C.—superior vena cava, C.S.—conorary sinus, T.V.—tricuspid valve with thickened free margin on the right.

FIG. 6.—Left ventricle opened to show the anterior cusp of the mitral valve. The cusp and chordae are thickened.

FIG. 7.—Myocardium of left ventricle showing an area of non-specific inflammatory infiltrate between the fibres. (×413.)

FIG. 8.—Muscular artery from the apex of the lung, which at this level is dilated, but the thickness of the muscular wall is double that of the control vessel at the same level. The reduced filling of small vessels in Fig. 10 is distal to this level. (×126.)

FIG. 9.—Muscular artery from the anterior basal segment at the periphery of the lung, which is constricted and shows a relatively thick media and intimal hyperplasia. (×126.)

[1] Bedford, D. E., Papp, C., and Parkinson, J., *Brit. Heart J.*, 1941, **3**, 37.
[2] Doyle, A. E., Goodwin, J. F., Harrison, C. V., and Steiner, R. E., ibid., 1957, **19**, 353.
[3] In a symposium, *Brit. J. Radiol.*, 1958, **31**, 170.
[4] Bedford, D. E., Sellors, T. H., Somerville, W., Belcher, J. R., and Besterman, E. M. M., *Lancet*, 1957, **1**, 1255.
[5] Nadas, A. S., and Alimurung, M. M., *Amer. Heart J.*, 1952, **43**, 691.

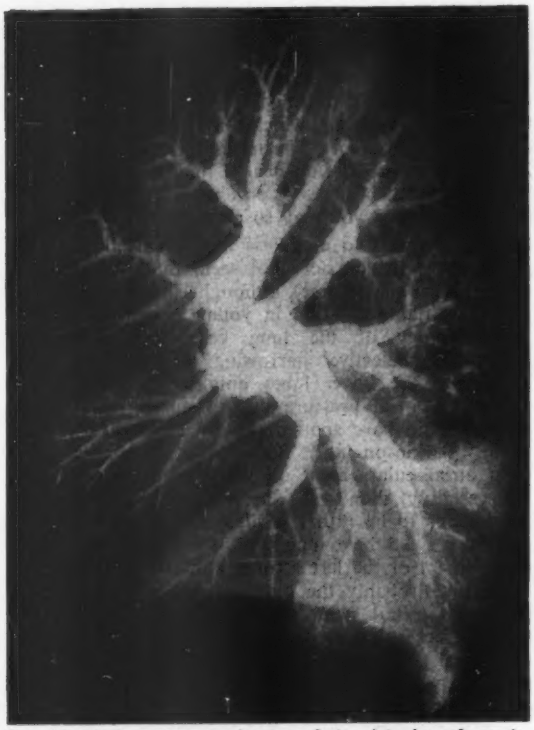


FIG. 10.—Post-mortem arteriogram of the right lung from the present case. Comparison with Fig. 11 shows dilatation of the main pulmonary artery and segmental branches. There is a reduction in the filling of muscular arteries in all zones, particularly marked in the lower zones of the lobes.

FIG. 11.—Post-mortem arteriogram of normal right lung for comparison with Fig. 10.

small pulmonary arteries, leading to the Eisenmenger syndrome with reversed shunt. Thrombosis of major and small pulmonary arteries is a not uncommon terminal, or pre-terminal, event in these patients.

The results of surgical treatment[4 6] are worth considering in this disease. The mortality is under 1% for good-risk cases, and around 12% for bad-risk cases. A large heart, mitral stenosis, congestive heart failure, atrial fibrillation, and a high pulmonary vascular resistance all increase the risk appreciably. Hypothermia is used in the uncomplicated cases, and the operation is well worth doing in younger patients who have none of these complications.

TERMINAL RESPIRATORY FAILURE

Dr. P. HUGH-JONES: I was asked to see this patient by Dr. Goodwin about the advisability of tracheostomy, and felt, on clinical grounds, that tracheostomy wasn't really justified. She was *in extremis* when I saw her, and she had had a rather sudden onset of this final collapse. I myself wondered whether she had had a pulmonary-artery thrombosis. She certainly seemed to have reversed her shunt through the atrial septal defect, and I thought that much of her cyanosis could well be accounted for by that. Undoubtedly she had severe pneumonia as well as her heart condition, and the question is what are the pros and cons of tracheostomy, with or without artificial ventilation, in such cases?

If they are hypoventilating, and especially if there is obstruction of the larger airways from excessive secretions which are not being coughed up, then tracheostomy can be of great benefit, and it is often done too late.

Functionally there are two states which may occur in pneumonia: one is alteration of gas and blood balance in the lungs, especially in parts with blood flow going on and little ventilation; the other may be overall hypoventilation. The first gives rise to hypoxia and if extreme to cyanosis, but rarely causes any carbon-dioxide retention. Effects can be relieved by giving oxygen. The second causes carbon-dioxide retention, and its presence may be an indication for tracheostomy. This patient had a raised serum bicarbonate, and therefore might very well have been in respiratory acidosis with hypoventilation. But she'd been vomiting, and a high bicarbonate can occur from metabolic causes—chloride loss, and so on. The critical test is measurement of the arterial carbon-dioxide tension. We failed to get arterial blood from her in her extreme state, and so tried to estimate the arterial carbon-dioxide tension by measurements of her expired gas. Rapid analysis of a single expirate, which we did, can be erroneous, since gas can come from relatively well ventilated parts of the lung, and, unless the patient can breathe out deeply, no "alveolar plateau" can really be measured. In any case the carbon-dioxide plateau is never flat, especially when there is much variation in ventilation–perfusion balance in the lungs. The better alternative is to use a technique whereby the patient rebreathes into a bag and the mixed venous carbon-dioxide level is measured from the equilibrated gas in the bag. This, less 6 mm. Hg, gives the arterial tension. In her case all our results suggested that she hadn't gross carbon-dioxide retention, though there was difficulty in assessing their accuracy in this very ill

[6] Swan, H., Kortz, A. B., Davies, D. H., and Blount, S. G., jun., *J. thorac. Surg.*, 1959, **37**, 52.

patient. On balance we felt tracheostomy not to be warranted: her sputum was not very thick, much of her cyanosis and extreme condition could have been due to her heart, and we didn't think she had gross carbon-dioxide retention.

With regard to Dr. Bishop's point about the lower-lobe vessels, I would like to suggest that the changes in the pulmonary arteries to the lower lobes were fairly long-standing and not likely to be connected with recent bronchopneumonia. I think our patient's mitral stenosis, though perhaps not surgically critical as defined at the present time, was sufficient to produce selective pulmonary artery changes.

Evidence of Rheumatic Carditis

Professor J. McMichael: Dr. Bishop showed us round-cell accumulations in the myocardium, but she did not call them Aschoff bodies. Were you really firm about that, or could they be?

Dr. Bishop: In the presence of bronchopneumonia I would rather hesitate to say so because, if you are going through the myocardium pretty carefully of any patient who has died of bronchopneumonia, you will quite often find cellular aggregates of just this kind, and there is no collagen necrosis or scarring of rheumatic type.

Professor McMichael: I see, they are not Aschoff bodies. The other point you emphasized was, of course, the localization of thickening of the chordae and the mitral valve to the edges, not at the base, which is also different from the ordinary appearances in rheumatic heart disease.

Dr. Bishop: Very much so.

Professor McMichael: So it is rather a peculiar form of mitral stenosis.

Anomalous Pulmonary Vascular Pattern

The other thing that rather worries me is the state of the vessels at the base of the lungs. We had been accepting the idea that in mitral stenosis this basal localization depends on higher pressures in that situation, but in this case there was a safety valve, as Dr. Goodwin has put it, through the hole, and there couldn't have been such an enormous elevation of pulmonary vascular pressures. What do you think, Professor Harrison?

Professor C. V. Harrison: I am as unhappy as you are. I was shown this film (Fig. 10) "blind" by Dr. Bishop, and I diagnosed it straight out as a mitral stenosis. Then it was pointed out to me that this really wouldn't hold water because the mitral valve wasn't tight enough, and anyway there was plenty of escape for it, and I said, "Well, perhaps it is only bronchopneumonia"—rather reluctantly. Then, of course, I come back and find that the darn thing was there in life. It was shown on an *in vivo* picture (Fig. 3a). So I am driven back again to the belief that this is something *real*. I still can't account for it.

Professor McMichael: Does it shake some of your interpretations of the sequence of events in mitral stenosis?

Professor Harrison: Definitely.

Professor McMichael: We were wondering if retardation of flow might initiate the development of obstructive vascular anatomical changes in the lower halves of the lungs. This woman had an enormous pulmonary flow until the very terminal stages, so that you couldn't say flow was retarded.

Professor Harrison: We have hitherto believed that this picture depended upon a back-pressure, a rise of pulmonary venous pressure. That has been the sort of keystone of our interpretation, and that is why this case gives us a great deal of food for thought. I think we have just got to keep our minds open and go on doing a lot more work. We thought we had got this buttoned up, and I am not so darned sure!

Dr. Goodwin: I don't think we have previously seen, in the same patient, this coincidence of mitral disease, which produces basal arterial changes because of raised pulmonary venous pressure, with atrial septal defect, which produces diffuse arterial changes because of the left-to-right shunt. The current concept is that the medial thickening of the pulmonary arteries in patients with left-to-right shunts is because the shunt itself in some way excites vasoconstriction, which is followed by hypertrophy. I suppose that it is possible here that you have got hyperdynamic hypertension and flow exciting diffuse vasoconstriction, and in addition you have got a rather higher level of pulmonary venous pressure than normal. Perhaps in the presence of increased flow, basal vasoconstriction is excited at a level of left atrial pressure much lower than would be expected with mitral stenosis alone.

Professor Harrison: I think the answer is that we have got to examine some more cases of this so-called Lutembacher's syndrome. This is the first case I have had an opportunity of seeing with a post-mortem pulmonary angiogram. If this turns up in the next case, then bronchopneumonia and all these other explanations have got to be abandoned, and we must accept it.

Dr. Goodwin: The difficulty is that it really is very rare—5% of all atrial septal defects.

Professor McMichael: I wonder if this isn't an instance in which we might approach some of the other centres of specialized cardiac surgery, where they must be seeing a lot of these cases, and ask if we could see the lungs?

Dr. Goodwin: I think we could do so, Sir.

Professor McMichael: I am sure they would be willing to help, because otherwise we shall get no further with this problem in our working lifetime.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

The *Annual Report for 1958–9* of the Nutrition Research Laboratories, Hyderabad, Deccan (Indian Council of Medical Research), explains that the laboratories moved to Hyderabad in December, 1958, and points out that the transfer of a well-established institution from one town to another 800 miles away must inevitably disrupt and delay scientific work. The work discussed in the report includes studies on protein, iron metabolism, and vitamins, and nutrition in pregnancy and lactation. During the year 129 requests were dealt with from the public and 90 requests from Governmental agencies for information and advice on diet and nutrition. A brochure was prepared for use in North India giving menus for cheap, balanced diets.

THE MEDICAL ADVISER

SEVENTH JAMES MACKENZIE LECTURE

On November 19, at B.M.A. House, Dr. LINDSEY BATTEN delivered the Seventh James Mackenzie Lecture of the College of General Practitioners. His subject was "The Medical Adviser."

Dr. Batten said he did not wish, that day, to argue the case for the general practitioner when engaged in his traditional pursuits of diagnosis, prognosis, and treatment, or to forecast his future, but to concern himself with another of the general practitioner's manifestations, that of adviser; adviser not to collective bodies—the Treasury, an army, factory, borough, or school—but to single individuals or at most to families. Doctors of his own vintage had had on the whole a very creditable medical education, but, for all that, they had not been told they would be constantly asked for advice nor taught how to give it. Then and, as he suspected, now, they had to find out for themselves.

Premarital Advice

He would begin, not with the mewling infant—that would come later—but with the lover, in the shape of a young man or woman intending to marry, or the engaged couple complete, coming to see the doctor about it, seeking, in current phrase, premarital advice. He would make no attempt to cover the ground, which had been pretty thoroughly tilled by others. But the medical had at least one advantage over the non-medical counsellor. He could lead off with a physical examination like that for life insurance—searching, perhaps, but not highly charged with emotion—and whatever advice or counsel he had to give could spring unembarrassingly out of this examination.

Let them suppose that in the course of examination it turned out that one of the couple had sugar in the urine and proved to be diabetic. What then? We had, of course, considerable control over the disease, but we could not cure it and many of its "sidelines" were persistent, intractable, distressing, and disabling. The young patient might well believe "it's all right now. There's insulin." Alas, we knew better. We knew, too, that it was inheritable and was increasing among us—a "side-effect" of insulin's life-prolonging power. He had heard a consulting physician suggest that diabetics should not have children, and an American writer on medicine and morals who held that babies had a right to be born free of what he called a "taint" would without doubt agree. Must our adviser tell these young people that if they ventured on marriage they should keep it childless, or even that they should not venture at all?

It was well for the medical adviser that his job was to advise, not to give orders or pass judgment. In the case stated and in many parallel cases his duty seemed clear enough. It was to put the truth, the relevant facts, before those consulting him, not confusing theory or surmise with fact or probabilities with certainties, nor letting it be thought that medical considerations must outweigh other kinds, and then, quite firmly, to put the decision where it belonged—with them. If pressed hard to say what he would do in the like case, the doctor should give an honest answer but still make it clear that he spoke only for himself or, at most, was giving the answer of his profession. There could be no question of bringing tables of stone down from the mount.

Personally he might hope their couple would risk it, but it was not for him to tell them so. The adviser's advice was "to think it over and decide."

Pregnancy

Advice in pregnancy came next, and the personal medical adviser was at least as much needed in these days of antenatal clinics and books and pamphlets for expectant mothers as he had been before they existed. Sometimes, no doubt, that splendid serenity of mind and conscious wellbeing that set in about the third month might breed in the mother-to-be contempt for the whole tribe of "antenatallers"—especially if she had trod the path before—and carry her through to a happy issue with nothing more than the necessary physical checks on progress. But there were other times when, having read the little books, listened to friends, and attended clinics, the poor girl found herself more and more confused. Must she really weigh weekly and was it quite fatal to get plump? How, precisely, did the fat-free diet mix with all that milk? Must she boil her breakfast egg while she fried her husband's? Were all the little tablets really necessary? What, exactly, *was* the Rhesus factor and what *exactly* happened if? It was terribly hard to find the time for those contractings and relaxings. Must she really? To whom should she turn?

The answer was not the extension of broadcast medicine; it was the preservation and encouragement of the personal medical adviser. Only he, or she, could give this particular perplexed expectant mother the advice and comfort she needed and ought to have. Standardized advice was no good to her.

Infants and Toddlers

In the field of "infant welfare" there was almost a tragedy to be recorded—a Paradise lost, hard though perhaps not impossible to regain. Here was a province of advisory medicine which, more perhaps than any other, the seeker for and the giver of advice could explore together to their great mutual advantage. Only a confirmed bachelor-doctor, misogynist and paedophobe, had nothing to give or gain. Erudition was not required. Common observation, common sense, a capacity for not being blown about by every wind of doctrine, and a quite small fund of apposite knowledge would suffice. For example, the two words "enough milk" comprised quite eight-tenths of the sacred mystery of baby-feeding.

It was the same with the "toddlers." They composed and performed their "variations on a nursery theme" long before Dohnányi, and they gave innumerable performances year after year yet never missed their intended effect. "Not use my pot," "not eat my dinner," "not go to sleep" comprised the whole thematic material—it could even be shortened to "not"; but so fertile were they in invention, so adept in the devices of augmentation, inversion, and ornament, that every mother believed her particular little fiend to be playing a new tune. The medical adviser could get quite a long way by assuring her, with conviction, that the theme had the widest currency and that even the present variant had been heard before. It was more than time that this fruitful and delightful field of advisory practice was reoccupied. It should never have been allowed to pass, by default, into other hands.

Youth and Invalidism

Youth was the time when people should be, and often were, at their healthiest, and when they should, and often did, have least need of a medical adviser. But it was also the time when, notoriously, introspection budded and bloomed, when doubts about the integrity of vital organs were sown or sowed themselves and all too easily took root. Hearts and circulations, lungs and generative organs were the commonest objects of apprehension; brains and livers generally received the confidence in their integrity they well deserved; and so, at this age, did the alimentary system (its turn came later). Of course there was commonly an iatrogenic factor, direct or indirect, and ironically enough the deadly seed might be sown by an examination, a "keeping under observation," or a restriction of activity decreed in the name of preventive medicine or by some ill-conceived piece of "health-talk," printed or broadcast.

Here, in chronic invalidism, cardiac or other, was a common and most important field of action for the medical adviser, for it was rarely possible for anyone else to uproot the seedlings of this disorder, and if not uprooted young they were commonly un-uprootable. It might take two

to do the job—a family doctor and a consultant—but for success they must work in the closest of close harmony. Even if it took two it remained a personal task for which teams and institutions were wholly unfitted. Often enough, only the personal doctor had a chance. And what chance had he? What was known about chronic invalidism—its origins, incidence, in terms of age, sex, social class, income, occupation, and place of residence; of its natural history, relation to organic disease, and response to treatment? Yet the rare success was very rewarding. To deflect a potentially useful fellow citizen from the dismal round of investigation, reinvestigation, and constant or recurrent therapeusis, to convince a young doubter that his heart—for example—was as strong and unstrainable as a heart could be, gave as full and lasting satisfaction as did the saving of a life physically endangered.

If it were said, "But this is psychiatry, and in a properly organized medical service would fall to the psychiatrist," the answers were that, if a young man thought his heart was at fault, the last kind of specialist he would see was the one he might call a trick-cyclist—a heart surgeon would be more to his taste—and, even if he would, there were never likely to be enough psychiatrists to go round.

Middle Age and Death

An advice-book on middle age he had read implied that, for most, middle age was a dreary hinterland between "those blue remembered hills" of youth and the swamps or rocks of age. He had not found it so, and he hoped he was not exceptional. But, flat or not, it contained for the medical adviser one unique and notable feature—the menopause. A male adviser, immune from direct experience, must needs speak with diffidence, but might feel able to tell the anxious inquirer that neither suicidal nor murderous impulses, not even mistaking red traffic lights for green, were necessary ingredients, and that it was quite common to emerge recognizably still oneself. If he did feel thus able, what he said was often well received and might come more comfortingly from him than from the little books or from "this column"—even if it was to be found there—but was he justified? "Frankly, I do not know," said Dr. Batten. "I suggest that here, in the symptomatology of the uncomplicated menopause, is a worthy subject for general-practitioner research."

If, as John Morley had said, "the great business of life is to be, to do, to do without, and to depart," the medical adviser could help considerably in the last two undertakings. It did help old people to know that many minor losses—loss of balance, of high-tone hearing, of undazzled vision against the light, of memory for names and things just done, of ability to keep warm and keep awake, of agility and physical endurance—were common to most of us in age and must, within reason, be accepted, though they could often be dodged or compensated.

Lastly, departing. Here practical help in smoothing the path rather than words was likely to be demanded of the medical man, but there was still a place for advice. "To tell or not to tell" would turn up time and again. He wished only to say that he was sure the words "always" and "never" were equally out of place; he was sure the *ideal* was for everyone concerned to be courageously "in the know" together, facing death open-eyed, and he was sure that though this ideal was often unattainable it should not on that account be abandoned.

In conclusion, Dr. Batten said he hoped he had convinced any who needed convincing that there was a field of medicine which was the medical adviser's very own, in which only he could effectively work, and that he and the work he did together constituted "a good thing" and should therefore continue to exist. But would they? A quiet unintended liquidation seemed such a likely fate. Suppose him gone and his works with him, the mortality rate would be quite and the morbidity almost unaffected. Those accustomed to consult him or brought up to count on him would, for a time, "feel quite lost," but this would pass; there would be no public outcry for his re-establishment and the Ministry would not notice the difference. The fragmentation of medicine, the adulation of teamwork, the curious belief that uniformity was somehow identical with justice, the unquestionable fact that he was, as they say, "uneconomic"—all these militated against him. His chances seemed poor, and yet, if he went, the sum of human unhappiness, great enough already, would be greater, and the satisfaction of medical practice to the practitioner would be less.

COLLEGE OF GENERAL PRACTITIONERS

EIGHTH ANNUAL MEETING

The annual general meeting of the College of General Practitioners was held at B.M.A. House on November 19—the College's eighth birthday. About 200 members and associates attended. Dr. ANNIS GILLIE, chairman of council, presenting the annual report, described the consolidation and steady progress of the College. More than 6,000 members and associates had joined since its foundation—nearly 700 during the past year. There were now 35 faculties: 25 in the United Kingdom and Eire, four in New Zealand, one in Kenya, and five in South Africa where a South African council of the College was soon to be formed. During 1960 many members of council had travelled overseas, and general practitioners from New Zealand, Australia, Africa, Canada, and the U.S.A. had visited the College and attended meetings of council. Members and associates had represented the College, or general practice as a whole, on committees and working parties of many organizations within the profession. Several joint conferences had been held in different parts of the country; applications by family doctors for most of these had exceeded the possible accommodation.

Education and Research

Dr. Gillie drew attention to the many activities of the Scottish and New Zealand councils. She discussed the work of the Board of Censors, and its interviewing of candidates for membership of the College. The Research Committee of Council had been as energetic as usual, and had widened its influence and its range of work. The Register of Faculty Research had been extended to include research by faculties overseas. The Statistical Advisory Unit, made possible by a generous grant from the Nuffield Provincial Hospitals' Trust, would be of great value in future. The Undergraduate and Postgraduate Education Committees of Council had done more good work improving liaison between medical students and the faculties of the College, and extending the continuing education of general practitioners. 150,000 of the College's obstetric cards had been sold, and 30,000 summary cards; other cards to help family doctors in their clinical work were being prepared for circulation with the College journal. The Medical Recording Service had stimulated reading, study, and thought by many doctors working in isolated areas. Overseas Travelling Fellowships for General Practitioners for the next four years had been organized and financed by the Nuffield Foundation at a cost of £50,000, and were being administered in conjunction with the College. The Publications Committee, the Practice Equipment and Premises Committee (with its exhibition room at College headquarters), the Library Committee (with its photocopying service), the Ethical Committee, and the Assessment of Quality in General Practice Committee had all met several times. The work of the Appeal Committee, under the supervision of Sir Harry Jephcott and with much help from him, had raised £345,000 in a few months. Work on behalf of the appeal was now being extended to faculty boards. Dr. Gillie concluded by saying that the year 1960

had been an exceptional one for the College, which had proved itself to be a body of immense vitality and potential, whose opportunities and horizons were widening every month.

Elections and Presentations

Dr. G. F. Abercrombie was unanimously re-elected president for 1960–1. Sir Harry Jephcott was appointed an honorary fellow of the College. Dr. G. L. Hindson (Northumberland) was presented with the Butterworth gold medal (1959–60) for an essay on "Television and Health." The subject for the 1960–1 Butterworth gold medal will be "Future Trends in General Practice" (essays must be submitted to the chairman of the awards committee not later than September 30, 1961) and for 1961–2 "The Evaluation and Management of Backache in General Practice."

16 Upjohn Travelling Fellowships (up to £200 each) were presented to: S. N. Cole, J. L. England, M. E. Gordon, C. W. Grant, R. Guest Gornall, L. S. Henry, Agnes T. Kennie David Kyle, Alfred Model, P. G. Murphy, P. O'Brien, H. R. Playfair, L. D. Rutter, H. T. N. Sears, C. G. W. Sykes, and T. E. T. Weston.

Six Public Welfare Foundation prizes (£40 each) were presented to the following final-year students: Jean Draper and Margaret Ogden (Manchester University), N. E. Jensen (Guy's Hospital), I. L. Mackenzie (Sheffield University), B. A. Wharton (Birmingham University), and Janet Young (Edinburgh University).

The following faculty representatives were appointed to the next College council (1960–1): S. J. Carne (North London), G. S. R. Little (South London), E. A. W. Marien (East London), R. Cove-Smith (West London), George Swift (South-east England), D. G. Wilson (Northern Home Counties), W. G. Tait (Thames Valley), J. C. Leedham-Green (East Anglia), R. M. S. McConaghey (South-west England), D. L. Crombie (Midland), K. M. Foster (North Midlands), R. A. Murray Scott (Yorkshire), S. Freeman (North-west England), G. L. Hindson (North-east England), W. L. Selkirk (Merseyside and North Wales), J. N. M. Parry (Welsh faculty), Richard Scott (South-east Scotland), W. S. Gardner (West of Scotland), J. M. Henderson (East Scotland), J. A. Shearer (North-east Scotland), G. H. Clement (North Scotland), A. S. Boyd (Northern Ireland), J. I. O'Sullivan (South Ireland), V. G. Doyle (East of Ireland), J. P. J. Little (West Ireland), A. B. Jameson (Auckland), L. H. Cordery (Canterbury), H. E. M. Williams (Otago), A. A. Tennent (Wellington), Mary Robertson-Glasgow (Kenya), D. H. Pirie (Witwatersrand), I. Wolfsohn (Cape of Good Hope), A. J. Biesman-Simons (East Cape), E. W. S. Deale (Natal Coastal faculty), and J. F. Krige (Orange Free State faculty). Four elected members of council to replace those retiring were appointed: Annis Gillie, I. D. Grant, J. H. Hunt, and A. Talbot Rogers.

College Business

Two steps of major importance in the development of the College were taken at the meeting, which approved unanimously two resolutions—one about incorporation, the other concerning a Research Foundation. General agreement was obtained to the proposed memorandum and articles of association of the new incorporated College. Discussions took place on the publication of the first seven James Mackenzie lectures, and on the collection of 8-mm. films on subjects of interest to general practitioners.

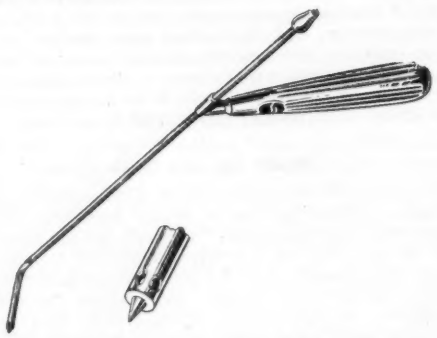
Dr. K. M. FOSTER moved a vote of thanks to the chairman, and to the British Medical Association for the use of its hall. At a meeting of the new council, held later, Dr. Annis Gillie was appointed chairman, Dr. K. M. Foster deputy chairman, Dr. H. L. Glyn Hughes honorary treasurer, and Dr. J. H. Hunt honorary secretary. Drs. J. F. Burdon, W. V. Howells, and L. Lamont were appointed additional members of council. On the following day 270 general practitioners attended a symposium on "Mental Health and the Family Doctor" organized by the College, sponsored by the Wellcome Foundation, and held under the chairmanship of Dr. G. F. Abercrombie and Sir Aubrey Lewis.

The Sugar Industry Labour Welfare Fund Committee in Mauritius has recently opened its thirteenth Social Welfare Centre there. The centre includes accommodation for maternity and child welfare services.

New Appliances

A FOREWATER PERFORATOR

Mr. J. G. DUMOULIN, consultant obstetrician and gynaecologist, South Devon and East Cornwall, writes: In surgical induction of labour, many obstetricians believe that forewater rupture is preferable to the rupture of the hindwaters. It seems to be safer and more efficient. Nevertheless, the Drew Smythe catheter is still probably used more than any other instrument for inducing labour. The reason for this is that it is the easiest to use, and there is no completely satisfactory instrument with which the forewaters can be broken. For this reason, I have designed the perforator illustrated.



To use it, two fingers are inserted into the vagina, the middle finger being placed at or through the external cervical os. The perforator is guided along this finger through the cervical canal posteriorly. The hand is withdrawn. The point of the instrument is rotated by moving the handle up and down. The forewaters are ruptured by this scratching movement.

This instrument simplifies a procedure that is sometimes not otherwise easy, and it does not damage the foetus. It was kindly made for me by Messrs. John Bell & Croyden, 52 Wigmore Street, London W.1, from whom it may be bought for three guineas.

Nova et Vetera

DAUGHTER OF DEBATE

Sir Arthur MacNalty, well known for his writings on Henry VIII and Elizabeth I, has now completed the trilogy by this volume on Mary Queen of Scots,* whom he well designates "the daughter of debate." The book, the result of several years' study of the literature and of original sources, constitutes a valuable contribution to the subject.

The story is well told and progresses from one dramatic crisis to another with the inevitability of a Greek tragedy—the murder of Rizzio, the abduction by Bothwell and the slaughter of Darnley, the Ridolphi and the Babington plots and the ultimate sad scenes, the trial and execution of Queen Mary herself, which the author describes in simple and very moving language. Surely no one was ever better qualified to write that essay on the uses of adversity which the Queen began, but never completed. There are several

(*Continued at foot of next page*)

**Mary Queen of Scots. The Daughter of Debate.* By Sir Arthur Salusbury MacNalty, K.C.B., M.A., M.D.(Oxon.), F.R.C.P., F.R.C.S. (Pp. 247. 21s.) London: Christopher Johnson Publishers Ltd. 1960.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

16-Epi-oestriol

"Actriol" (Organon).

Composition.—This is a bland cream incorporating 16-epi-oestriol, an oestrogenic substance.

Pharmacology.—Experiments on animals have shown that this oestrogen is absorbed through the skin and that application of it suppresses the activity of sebaceous glands. This is hardly sufficient by itself to vouch for its effectiveness in the treatment of acne in the human subject. Adolescents may have excessively greasy skins without acne, so that overactivity of the sebaceous glands can hardly be the one essential factor in all cases. Though the systemic administration of oestrogens will often improve acne, such large doses may be required that this treatment is not often of practical value. On the whole, the treatment of acne vulgaris by endocrine substances has been in most hands surprisingly disappointing.

Therapy.—It is suggested that the local application of actriol to the skin can bring a concentration of oestrogen to it which will abolish acne and will give rise to no systemic effects. In view of past experience with other types of hormonal treatments this claim must necessarily be regarded with reserve. It is, however, not unreasonable, and the preparation merits careful clinical assessment. Any treatment for acne needs to be continued for several months and assessed with great care, because improvement is likely to be slow and because of the spontaneous fluctuations in severity to which the disorder is usually subject. So far there has hardly been time for actriol to be thoroughly assessed. Some hospital trials are being carried out, and presumably a critical evaluation will be possible in due course. In the meantime treatment with actriol is perhaps best limited to those patients who can be expected to carry out the treatment consistently and to be available over a period of many months so that the effect of treatment can be carefully judged.

N.H.S. Basic Price.—15 g., 10s.

(*Continued from preceding page*)

appendices, of which the first, dealing with the various illnesses from which the Queen of Scots suffered, is of unique value.

Sir Arthur looks at the life of his heroine through medical and slightly rose-tinted glasses, though he confesses that Mary Stuart was never wise, and allows that she made solemn promises which she had no intention of keeping. In this she was but in keeping with her times, when treachery and lying were frequent in diplomatic dealings. Yet her seventy different ciphers did not hide her secrets from the astute Walsingham. The author's special knowledge enables him to point out that one of the reasons for the frequent change of the place of captivity was the fact that such residences soon became noisome owing to defective sanitation, and intervals for periodic cleansing were necessary. One incidental fact of great interest is mentioned (p. 32), that Mary Queen of Scots was responsible for the founding of the straw-hat industry in this country.

No historian can afford to miss this interesting volume in which can be traced the influence of an ailing body upon the actions of a famous but unfortunate historical personage.

ZACHARY COPE.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Prescribing Costs

SIR,—I would like to congratulate Drs. Alistair Mair, George B. Mair, and Andrew Taylor on their most interesting article on prescribing costs (November 12, p. 1442). I think that their point about referring acute cases to hospital deserves emphasis. A case of pneumonia treated at home may require an expensive antibiotic, as well as analgesics, sedatives, cough linctus, etc. Eight or ten prescriptions in all might be required. But what would a hospital bed for two or three weeks for this same patient cost the State?

To worry or criticize general practitioners for the high cost of their prescribing alone seems to me to be quite illogical. The type of practice (rural or industrial), the age-incidence, the readiness of the doctor to treat his patients at home, are only some of the points which must be closely associated with his prescribing costs. Finally, in this scientific age the patient's faith in his bottle of medicine is a truly wonderful thing. It is a faith that our profession has encouraged in the past. I am not sure that it is wise to be too precipitate in discouraging it now.—I am, etc.,

Dalkeith, Midlothian. H. M. S. NOBLE.

SIR,—During 25 years under the umbrella of Lloyd George and 10 in the shadow of Aneurin Bevan, I was twice called to account for overprescribing. The first occasion, in my youth, brought upon me a courteous gentleman from the Ministry who pointed out that I had occasionally prescribed 5-grain tablets of calomel. If I were sure it would not be to the detriment of my patients, could I in future prescribe 4-grain tablets and save the taxpayer's money?

Proud of the efficiency of a department which concerned itself over such minutiae, I was careful for many years. Then, in middle age, I was again hauled over the coals. I had prescribed a proprietary lotion which, unknown to me, was scented. This made it a cosmetic and so not available to the suffering masses. I regret that this time I guffawed. But no one had ever told me just how extravagant I was. Till, one day, there did arrive a piece of paper informing me that my prescribing costs were 70% of the area average. I looked forward to getting, under separate cover, either an illuminated testimonial, or at least a bottle of whisky. Not even a pat on the back. Ah me!

Being now on the side lines and able to take an impartial view, I am compelled to the conclusion that the Ministry know nothing about prescribing at all, and it might be a good idea if, instead of persecuting those whose costs are high, they took some advice on the subject from those whose costs are low.—I am, etc.,

Ashtead, Surrey. W. EDWARDS.

SIR,—Fascinated as I was by the article by Drs. Alistair Mair, George B. Mair, and Andrew Taylor on prescribing costs (November 12, p. 1442), I cannot but feel that they have been misled by fallacious statistics into implying that their colleagues have been

seriously underprescribing. It seems likely that the excess cost arises from a difference in the age-structure and composition of their practice rather than a difference in prescribing habits. Possibly their practice grew rapidly some 30 years ago, remained stationary, and has now again entered on a stage of rapid expansion during which, because of their clear interest in emotional disorders, they have accepted many patients with anxiety states. This will have left them with a practice containing many old people and many requiring much time and treatment and will lead to apparently excessive costs.

It is impossible to obtain figures comparing the age-structure and nervousness of a practice, but it is easy to compare the death-rate in a practice with the local mortality-rate. Over a period of years the death-rate of a practice will depend almost entirely on the age-structure of that practice. These figures can be worked out in a few hours, and I believe they will find that their death-rate will exceed the local death-rate in much the same proportion as their prescribing costs. These figures will be unanswerable when they next meet the local medical committee.

Finally, may I protest, Sir, at the way these meaningless costing figures are used to badger general practitioners?—I am, etc.,

Rugby, Warwickshire. S. CLIFFORD ROGERS.

White Mouse Medicine

SIR,—Dr. Hugh Sinclair (November 19, p. 1520) disagrees with my advocacy of animal fats. That does not surprise me, but I find the sneers with which he voices this disapproval a little cheap for an Oxford don. He was unable to find the article in a library; yet a day before it was published he told a London journalist that he did not think I knew much about the subject (*Daily Mail*, October 13). He treats my article as an attack on research. My views on animal experiments have been published.[1] They are as follows:

"Experiments are of value only if the circumstances chosen by the experimenter are the same, or nearly the same, as those of the problem to which he is seeking an answer. The mystery of the loss of the Comet was solved by subjecting another Comet to stresses similar to those which the lost airliner might have encountered; it would never have been found by experiments with a motor-car or a submarine. The problem of peptic ulceration will be solved by observation of the experiments that men make on themselves, not by experiments on creatures whose habits, diet, and digestive apparatus are entirely different from our own."

He finds me illiterate. My reading has not been wide: it certainly does not include *Epidem. Vital Statist. Rep.*, but it will do so if I can find one in my library. I cannot spell. It is true that I left one s out of Stefansson's name, but I reported his views correctly, and they agree with mine. He may say that the Eskimos have never heard of butter. Why should they? They have never seen a cow, but they get all the animal fats they need from blubber, and they thrive on it.

The only thing I regret is my use of the phrase "commercial racket." The British pharmaceutical industry, as is well known, exacts high ethical standards, but it is not as altruistic as Sinclair claims, nor as foolish as he seems to believe. A firm of sufficient financial standing to be prepared to invest more than £2m. on the advice of a laboratory scientist will have decided, after careful costing and market research, that they stand to make at least £200,000 a year in the way of increased earnings yield. The gain may not be in the sale of "helpful fats" to food faddists and cardiac neurotics. The big money comes in the expanding production and increasing use of vegetable oils, which are needed in enormous quantities by the soap, confectionery, and cosmetic industries.—I am, etc.,

London W 1. HENEAGE OGILVIE.

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"Celbenin" and Probenecid

SIR,—In an orthopaedic hospital patients for whom we may wish to use "celbenin" (BRL 1241) are likely to have chronic bone infection and require treatment for a considerable number of weeks or months. Apart from the discomfort and difficulty of continuing four-hourly or six-hourly intramuscular or intravenous injections for such periods, long treatment can cause local reactions.[1,2] It occurred to us that we might reduce the rate of excretion of celbenin by the use of probenecid, as is the case with the earlier penicillins, and reduce the frequency of injections if therapeutic blood levels could be maintained for a reasonable number of hours. Dr. E. T. Knudsen, of Beecham Research Laboratories, kindly supplied us with material before the product was on the market, and we were able to check the blood levels in several patients with different dosage with and without probenecid given 0.5 g. half to one hour before the intramuscular injections.

Previous investigations have shown that the serum concentrations after 1 g. intramuscularly are around 12 μg./ml. at one hour and down to 2 μg. at four hours and zero at six hours. We obtained similar figures without probenecid, but with probenecid the figures at one hour were 32 to 64 μg./ml., and therapeutic blood levels of 4 to 16 μg./ml. (usually about 8 μg./ml.) were still present at eight hours. The penicillin assay was carried out by a tube titration method using doubling dilutions of patients' serum in broth. Nutrient agar seeded with *Staph. lactis* was added afterwards and the tubes sloped. The results were calculated by comparison with a row of similarly prepared standard dilutions of celbenin. The number of our patients (4) and the number of our estimations (19) are both small, but the results would clearly seem to indicate that the method is worth pursuing.—We are, etc.,

F. HARWOOD STEVENSON.
K. JOY HARRISON.

Royal National Orthopaedic Hospital, Stanmore, Middlesex.

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Congenital Deformity

SIR,—Mr. Denis Browne has in the past done a great service in improving the understanding of congenital deformities by his stimulating, even provocative, studies. In his letter (November 12, p. 1450), and in others before, he is not fair in regarding other workers as being unprogressive and scientifically blind, nor in regarding himself as a persecuted prophet. It is simply untrue to say that there is "a present refusal of orthopaedic surgeons to consider intrauterine mechanics" as an influence in certain compression deformities. Murk Jansen in his *Feebleness of Growth and Congenital Dwarfism*[1] made much of the influence of amniotic pressure. In the foreword to this book Robert Jones says that the work displays "a new line of research both fascinating and scientific, and of great social and practical promise." Denis Browne has carried

the promise to fruition and his methods are practised extensively by orthopaedic surgeons, at any rate in Great Britain; and critically, as I am sure he would wish. As recently as 1959[2] I surveyed this field and gave credit to Denis Browne's views.

In the future we shall look further than amniotic pressure as a cause of deformity. After all, the amnion is, like the chorion, an embryonic structure formed from the same primordial cells as the foetus. What are the hereditary and environmental factors which cause amniotic and other foetal defects? Recent work on teratology is helpful. For example, Ingalls, of Boston, writes[3]: "From the welter of investigations has come an ever-growing list of teratogenic agents . . . mechanical, thermal, electrical and radiant." (He includes a large number of chemicals.) "The very diversity . . . suggests that any substance that can kill, can induce abnormal growth when acting in critical dosage at an appropriate moment of development." Ingalls was in particular studying the effect of maternal anoxia at a critical period of gestation.

Mr. Denis Browne has taught us much, but the future lies elsewhere: in the preventive possibilities which will come from the scientific study of fundamental aetiology. —I am, etc.,

Exeter, Devon. NORMAN CAPENER.

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Natural Gas

SIR,—In recent weeks two installations have come into operation in the British Isles to modify natural gas and supply it to domestic users through the town mains in place of coal-gas. In Guernsey imported compressed (presumably liquid) butane is used; in Whitby the gas is drawn directly from a nearby underground source. In each case the hydrocarbon gas is heated with steam to give a mixture of hydrogen and carbon monoxide; this is then diluted with certain products of combustion. The object of these operations is to reduce the calorific value of the gas to a value comparable with that of coal-gas. From the medical point of view their effect is to convert an almost harmless gas into a lethally toxic mixture similar to the domestic coal-gas in current use which, in 1958, in England and Wales, was responsible for 2,637 deaths from suicide and "self-inflicted injury" and 870 accidental deaths.[1] It may be claimed that many of those committing suicide would have chosen another agent had gas not been available, but for the accidental deaths at least gas is entirely responsible. The figure for the latter, moreover, is more than double that for 1949, so that it is not unlikely to increase still further.

If the installation of the new process were to be confined to a few small towns its effects, though deplorable, might be limited to the continuing occurrence of a few deaths a year, similar in number to those which would otherwise have been caused by coal-gas. There are, however, indications that in the next few decades domestic gas will be derived more and more from natural-gas sources. It may be that the larger gas-undertakings already have plans for the use of unmodified or only slightly modified natural gas, but it is clear from the examples given that the method of processing needs to be considered from a national point of view at the present time, before large amounts of capital are sunk in new plants.

There is no doubt, as country users of "calor gas" well know, that pure hydrocarbon gas can be used successfully and conveniently for domestic heating and cooking. Presumably a change to the supplying of such gas by public gas-undertakings, while avoiding the installation of expensive processing plant, would necessitate the adjustment or replacement of all burners and perhaps other technical adjustments. The question to be decided nationally is whether the cost involved is worth while in order to reduce and ultimately to eliminate a national death roll of 3,000 persons a year. —I am, etc.,

London S.W.15. A. E. MOURANT.

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Surgical Treatment of Parkinsonism

SIR,—The observation of Mr. F. J. Gillingham and his colleagues (November 12, p. 1395) that operation for Parkinsonism led to improvement in the associated diabetes mellitus of one of their patients is, as they say, of considerable interest—for two reasons. Firstly, the occasional association of diabetes mellitus with functional impairment of the central nervous system and especially the hypothalamus, both in man and in the experimental animal, is well recognized,[1 2] though a precise causal relationship has not yet been established. By contrast, attempts to relieve diabetes mellitus in the experimental animal by neurosurgical means have failed, with one notable and controversial exception.[3] Secondly, the question arises as to the significance of the diabetes mellitus in this particular patient with Parkinsonism. Twenty-five years ago Lewy and Gassman[4] stated that "alimentary hyperglycaemia" might occur in this disease, and pointed out that the periventricular nucleus of the hypothalamus (experimental destruction of which was commonly accompanied by hyperglycaemia) was frequently involved in the disease process. So far as we know these observations have not been followed up.

In the past six months one of us (R. O. G.) has treated 88 patients suffering from Parkinson's disease with chlorpropamide, a substance originally introduced as an oral antidiabetic agent. This drug either alone or in combination with other drugs has a most pronounced anti-Parkinson effect in certain patients, and preliminary results are given in the accompanying table.

TABLE

Total No. of patients treated with chlorpropamide	88
Improved with chlorpropamide alone or combined with other drugs	50
Failed with chlorpropamide alone or combined with other drugs	20
Given chlorpropamide because other drugs disappointing	18
No. in latter group who improved	8

Of the 30 failures, 13 were unresponsive or became worse, seven complained of dizziness and four of heavy sweating in spite of normal blood sugars, and two each developed hypoglycaemic attacks, confusion, and tiredness.

A number of questions arise as a result of these various observations. Does chlorpropamide act on the central nervous system in a manner similar to thermal electrocoagulation? Should diabetes mellitus occurring

in a patient with Parkinsonism be regarded as an added indication for neurosurgical treatment? And finally, is there an association between diabetes mellitus and Parkinsonism? In order to answer the last question a survey of carbohydrate tolerance in patients attending the Parkinson clinic at this hospital has already been planned.—We are, etc.,

R. O. GILLHESPY.
A. PATON.

Dudley Road Hospital,
Birmingham 18.

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SIR,—As a patient of Mr. F. J. Gillingham's I should like to add a postscript to his excellent article, written in collaboration with Drs. W. S. Watson, A. A. Donaldson, and J. A. L. Naughton, on surgical treatment of Parkinsonism (November 12, p. 1395).

I developed Parkinsonism seven years ago at the age of 35. I have now had two operations as described in the *B.M.J.*, both done under local and completely painlessly. I would like to describe the thrill when the electrode entered the globus pallidus. I felt at once complete freedom of movement in the contralateral limbs together with the whole freeing of the mind as well, so much so that I became very garrulous and somehow felt wonderful. It was as if I had been freed from a bondage of five years' duration. At the second operation I did not feel this intense euphoria at the liberation of my other limbs I suppose by this time I was more blasé about it, and expected it, but it nevertheless occurred just as it did in the first instance. I might add that I am now doing full-time work.—I am, etc.,

Yeovil, Somerset. ARNOLD H. BANTON.

Cycloserine in Urinary Infections

SIR,—In their letter (November 5, p. 1383) Drs. J. McC. Murdoch, S. C. Frazer, and J. D. Sleigh suggest that the "very high" minimum inhibitory concentrations of cycloserine required for *E. coli* in our series (October 22, p. 1191) might have been due to the use of a different salt of cycloserine in the sensitivity tests. This, in fact, was not the case. The "special" salt of cycloserine was the ordinary substance supplied in a pure form by Eli Lilly & Co., Ltd., specially for sensitivity tests. It is, however, possible that the differences in technique might have influenced the results. In the tests carried out by Dr. Murdoch and his colleagues the inoculum was 0.02 ml. of a 1/250 dilution of overnight culture of *E. coli*, whereas in our tests 0.02 ml. of an undiluted culture was used.

We do not disagree about the efficiency of cycloserine in uncomplicated *E. coli* infections. Strains of this organism are, however, usually sensitive to many chemotherapeutic agents, and in view of the possibility of side-effects following the use of cycloserine, in our series 4/22, we consider that this drug should not be a first choice in these cases. Our main investigation was, however, with complicated cases, caused by organisms resistant to the usual range of agents, and which therefore constitute a serious problem.—We are, etc.,

R. W. FAIRBROTHER.
G. GARRETT.

Department of Clinical Pathology,
Manchester Royal Infirmary.

Hazards of Iron-dextran

SIR,—The description by Dr. T. S. Worthy and Mr. E. J. C. Wynne of a metastatic carcinoma at the site of injection of penicillin (October 22, p. 1208) prompts me to add a postscript to the case report by Robinson, Bell, and Sturdy,[1] entitled "Possible Association of Malignant Neoplasm with Iron-dextran Injection," the accompanying annotation,[2] and the subsequent correspondence.[3 4]

Through the courtesy of Dr. J. H. Sturdy we have submitted sections of the biopsy (S-60, 1910) and of the specimen obtained at operation (S-60, 2373) to Professor R. A. Willis. He has granted permission for the publication of his report, which is as follows: "I have examined the four slides which you have sent, two labelled S-60, 1910, and two labelled S-60, 2373. All of these show chronic inflammatory granulation tissue with histiocytes and phagocytic giant cells, associated with areas of subcutaneous fat necrosis, such as may result from injections of mildly irritant substances; none of them shows sarcoma or any other neoplasm."

Turning from man to mouse it is illuminating to compare the latest position in parallel experiments with iron-dextran carried out in mice by Dr. H. G. Richmond[5] and by ourselves. The following Table makes clear the striking concordance between the results of these two sets of experiments, carried out independently on different stock strains of mice. I understand from Dr. Richmond that he has since repeated his series of experiments in mice, with substantially similar results.

These findings clearly suggest that it is only at the very highest doses that tumours develop. The results differ considerably from those reported by Haddow and Horning,[6] who obtained the first sarcoma at 11 months and a total of 10 sarcomas in 15 mice which had received 13 weekly subcutaneous injections of 0.2 ml. iron-dextran. We have carried out an experiment with 250 mice of the stock Chester Beatty strain kindly

Mouse* Group	Material Injected	Intramuscular Injection: Weekly Dose (ml.)	Richmond Results[5]				Benger Results[7]		
			Duration of Treatment (months)	Total Dose	Number Surviving 12–15 months	Final Number of Sarcomas	Maximum Total Dose‡	Number Surviving 12 months	Final Number of Sarcomas
W	Iron-dextran	0·002	9	4·1 mg. Fe	35	0	8·0 mg. Fe	30	0
X	"	0·02	9	41 "	19	0	80 "	22	0
Y	"	0·1	6	145 "	24	0	290† "	2	1
Z	"	0·2	6	290† "	6	2	460 "	0	0
D	Low molecular-weight dextran	0·2	9	8·2 ml.	23	0	16·0 ml.	29	0
S	Saline	0·2	9	8·2 "	30	0	16·0 "	28	0

* A total of 50 mice of both sexes in each group. Strains used were: Richmond—S.A.S. (Schofield strain), Benger–Albino (Tuck No. 1 strain).
† Equivalent to a total dose of 14,500 ml. in man on the basis of body weight.
‡ The injections were continued until the death or sacrifice of the animal.

provided by Professor A. Haddow. The individual doses were the same as those listed in the table for groups W, X, Z, D, and S, but a total of 10 weekly intramuscular injections was given, 5 into each thigh. In fact, therefore, the highest dose administered into each of the two injection sites was 50 mg. Fe in our series, in contrast to 130 mg. Fe used by Haddow and Horning[6] in the same strain of mice. After 12 months the numbers of survivors in groups W, X, Z, D, and S were 21, 45, 13, 10, and 26 respectively. Now, after 18 months, there are 7, 15, 3, 5, and 11 left. No injection-site sarcoma has developed in any mouse.

I should like to thank Dr. H. G. Richmond for permission to quote his results.

—I am, etc.,

Benger Laboratories Ltd., Holmes Chapel, Cheshire. L. GOLBERG.

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Anaemia in Pregnancy

SIR,—I have read with much interest the article of Dr. C. Giles and Mr. Harold Burton entitled "Observations on Prevention and Diagnosis of Anaemia in Pregnancy" (August 27, p. 636). In this hospital group for the past three years tab. folic acid and cap. vitaminorum t.i.d. have been prescribed for all pregnant women in addition to oral iron.

Recently I had considered using a proprietary preparation in an attempt to lessen the total number of tablets to be taken daily and to reduce the cost of the prescription, as a combined tablet means that there is only one dispensing and container fee instead of three. However, I was alarmed to find that the price of tab. folic acid varied from approximately 2s. 6d. to 10s. per 100 (basic N.H.S. cost). Hospital prices are, of course, much lower. I, with many of my colleagues, had understood that if a preparation was in the *National Formulary* then the cheapest tablet must be dispensed. It appears that this is not so. The chemist may dispense any manufacturer's tablet, code the prescription accordingly, and is paid for same though there may be many cheaper similar preparations.

Random sampling by the Pricing Bureau may reveal that a chemist is dispensing the dearer preparation persistently. He may then be warned to issue the cheaper preparation. To make sure that the cheapest tablet is always dispensed, it is necessary for the doctor to find out the name of the manufacturer and write his name on the prescription.

Giles and Burton recommended tab. ferrous sulphate because it was the cheapest iron preparation and as effective as the dearer forms. They made a plea that iron should be given without charge to all pregnant patients. I heartily support them. Tab. ferrous sulphate (basic N.H.S.) cost approximately 6d. per 100, but when dispensed by a chemist the total cost to the Health Service is 2s. 6d., less the 1s. fee paid by the patient. If the tablets were given to the patients at the antenatal clinic for the fee of 1s. they could obtain 200 tablets without any significant cost to the hospital.

I trust that I am correct in my argument and that the cost to the Health Service of giving all pregnant women iron, folic acid, and vitamins could be very much reduced by giving out the tablets at the antenatal clinics or by the general practitioner actually prescribing the cheapest form of the preparation as indicated above.

The present situation needs clarification, as it is obvious that numerous non-medical problems bedevil the prescribing and dispensing of drugs.—I am, etc.,

Tyrone County Hospital, Omagh. JOHN F. O'SULLIVAN.

Lumps in the Breast

SIR,—For the past twenty years I have made it my practice, when convinced on clinical grounds that a lump in the breast was a cyst, to aspirate the cyst. I have no record of how many times this has been done, but it must now be in the region of some 500 cases. In almost every case aspiration got rid of the lump and no further treatment was necessary. Chronic mastitis is, of course, a progressive disease, but on only one occasion did the cyst recur in the same position in the breast. On only one other occasion has aspiration revealed the tell-tale blood-stained fluid which prompted me to open the swelling to find a carcinoma and carry on with a radical mastectomy.

Aspiration of cysts of the breast has a distinctive place in the treatment of such cysts, and I am quite convinced that mutilating surgery which is done is quite unnecessary at times. There are two points which must always be noted: (1) If the cyst fluid is blood-stained. (2) If the lump does not disappear after aspiration. In either case biopsy is necessary.—I am, etc.,

Salford Royal Hospital, Salford 3. ROBERT W. WYSE.

Congenital Biliary Atresia

SIR,—There are several aspects of the paper by Sir Roy Cameron and Mr. G. L. Bunton (October 29, p. 1253) which call for comment. The paper is welcome since it gives the first published evidence of virtually complete recovery of the liver from an anatomical as well as functional point of view after the relief of total biliary obstruction in infancy.

It is perhaps not surprising that inquiries among medical centres have failed to reveal a single pathologist who has seen sections before and after operation, since many surgeons would be reluctant to submit an apparently normal child to further exploration merely for the purpose of biopsy. Moreover, the chances of having to open the abdomen of such a child for other reasons are remote, and one presumes this lucky chance arose and was wisely taken. On the other hand, when the authors say that all the pathologists consulted "were quite emphatic that they had never encountered a subject thought to be suitable for operation" one at first assumes that they mean "suitable" in the sense of needing a further operation months or years after they have been cured. However, rereading the paragraph gives the impression that these pathologists had not seen a curable case, an impression heightened by reference to the second oldest children's hospital (Philadelphia) where there were three successful cases. I am sure this erroneous impression (unintentional as it probably is) should be corrected, for nearly every paediatric surgical centre of any size has one or more of these children living. I was sorry to see the opinion that "surgery

in treatment is not necessary in children with atresia who are seen early in life." Surely if there is *atresia*, the sooner operation is undertaken the better. If it is intended to say that children with undiagnosed *jaundice* should not be operated upon in the first two or three weeks of life, that is an entirely different matter. Undoubtedly operations will be done on patients with hepatitis, with obstruction within the liver and with obstruction in the extrahepatic biliary system. Merely awaiting a few more weeks or undertaking any known series of tests will not distinguish *for certain* neonatal hepatitis from atresia. Moreover, at operation the only course is not "a minute examination of the anatomy from the portal fissure down to the duodenum." In many cases of extrahepatic block the dilatation of the duct is easily distinguished (as apparently in Case 4). If it does not immediately come to notice, an operative cholangiogram and liver biopsy will together sort out most of the cases and the child with hepatitis will have been spared a major and possibly lethal operation. Confirmation of a single obstructive aetiology in this way would strengthen the hand of the surgeon in a subsequent elaborate search for some accessible part of the dilated biliary system. Surely this is a more "rational treatment of the condition" than that suggested by the authors.—I am, etc.,

The Children's Hospital, Sheffield 10. R. B. ZACHARY.

*** We showed Mr. Zachary's letter to Sir Roy Cameron and Mr. G. L. Bunton. Mr. Bunton replied as follows:

SIR,—Mr. R. B. Zachary is quite correct in his assumptions contained in the first part of his letter. His second point is, I am afraid, due to a misprint, the sentence "surgery in treatment is not necessary . . ." should have read "urgency in treatment . . ." As to the last point which he raises, the reason for my statement that careful dissection of the anatomy is necessary is simply that only in this way can tiny or abnormal bile ducts be recognized, which if present can, as he suggests—and as I also pointed out—be used for operative cholangiography.—I am, etc.,

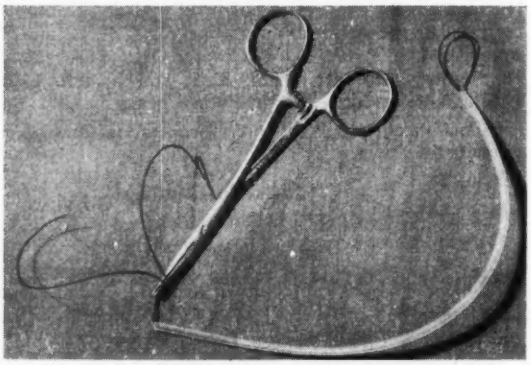
University College Hospital, London W.C.1. G. LOUIS BUNTON.

Operative Cholangiography

SIR,—I would like to comment on the technique for operative cholangiography described by Mr. James O. Robinson (October 29, p. 1291).

If the catheter is tied into the cystic duct the removal of this ligature prior to removal of the catheter can be a nuisance. I have devised the following method of overcoming this (see Fig.). A long catgut ligature is passed as usual round the cystic duct. Its ends are threaded through a piece of "polythene" tubing about 12 cm. long and 3 mm. in diameter. The exact measurements are unimportant. The ends of the ligature are clipped for security with a haemostat. The ureteric catheter is passed down the cystic duct into the common bile duct. The polythene is then pushed firmly up to the cystic duct and held tightly by clipping the ligature hard up against its distal end with a second haemostat. After the cholangiography the polythene is removed and the first half hitch tied round the cystic duct and catheter before removing the latter, thus minimizing any leakage of bile. The knot is, of course, completed after removal of the catheter, and the cystic duct divided in the usual way.

The second comment concerns the tilt to avoid superimposition of the shadows of the bile ducts and the vertebral column. If an estimate is desired of the degree of dilatation of the ducts, it is better that there should not be obliquity of the film to the *x* rays. The patient should be tilted before the operation by pillows



under the left shoulder and hip, and then levelled off by tilting the table to the left, for the actual operation. During the taking of the films the table is tilted back to the horizontal, so that the cassette is at right angles to the "line of fire." It is usually considered advisable to take more than one picture.—I am, etc.,

Newbridge, Wolverhampton. RONALD BENISON.

Hypertension in African Populations

SIR,—Dr. Alexander Walker and his colleagues from Johannesburg (September 10, p. 805) comment on contradictory views prevailing on hypertension in African populations. The mythical belief that hypertension, being largely a disease of "civilization," is not common in African populations dies hard in some quarters. It is refreshing to study the thoughts suggested by Dr. Walker's group.

In the context of East Africa, Professor A. W. Williams[1–3] has collected much data on the normal blood-pressure range in surveys of various tribal groups. The general impression gained from such population surveys was a trend towards a less marked rise in blood-pressures corresponding with advancing years than is observed amongst Europeans. There is reason to believe that there may be considerable regional differences within East Africa. Professor Williams is still engaged in further surveys. From hospital admissions it can be stated that hypertensive heart disease forms the largest group of patients with cardiac disease presenting at Mulago Hospital in Kampala, Uganda.[4] Much the same prevails on the coast at Mombasa.[5]

It is in respect of the aetiology of hypertension that much remains to be learnt in East Africa. At Mulago Hospital, the incidence of severe hypertension, especially in the young adult, has been challenging enough to merit the organization of a thriving hypertension clinic. It cannot be denied that the patients studied are a highly selective group, selected firstly from hospital in-patients and secondly for reasons of ease of follow-up,[6] but it can be stated that a striking feature is the high frequency of established renal failure in a large proportion of hypertensive patients when first seen. This and associated findings have led us to believe that in the clinic series approximately two-thirds of our patients are suffering from chronic renal hypertension.[7,8] At the same time there is an undoubted group of essential hypertension in both males and females.

Clearly, much remains to be done in the sorting out of aetiology of hypertension, renal *versus* essential, in our populations. The respective roles of pyelonephritis and glomerulonephritis are in need of closer study, and here we feel useful information could be gleaned in a careful pilot study of the hypertensive hospital patient and his environment. Any such study will have enormous application to the "civilized" world, but the complexity of these problems is such that short of measures in the form of World Health Organization sponsorship or Medical Research Council Social Medicine Unit sponsorship little can be deduced from the experiences of small clinics preoccupied with everyday therapeutic needs.—I am, etc.,

Mulago Hospital, Kampala, Uganda. K. SOMERS.

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Amphetamine in the Tropics

SIR,—I have followed with interest the annotation (August 20, p. 590) regarding the death of an athlete from amphetamine poisoning and the memorandum by Drs. S. C. Jordan and F. Hampson (September 17, p. 844) about a similar death.

In one of H.M. ships recently I visited a West African port and during our entertainment by the British residents was startled to see a tin of "dexedrine" (dexamphetamine) being handed around at midnight to facilitate continuation of their revels. This was regarded as a normal practice in a community tending to go in for marathon social activities at the week-end. The drug was freely obtainable, and I met several people who carried it for this purpose. So far as could be told, no major ill effects had as yet occurred, but it would be of great interest to investigate further cases of "heat exaustion" and "heat collapse" occurring among white people living in tropical conditions.—I am, etc.,

H.M.S. *Puma*. ROBERT S. H. TWIDLE.

Treatment of Skeletal Tuberculosis

SIR,—I would like to add my plea to that of Mr. M. C. Wilkinson (August 20, p. 598) to ask that consideration be given to adding surgery to the constitutional and antibiotic treatment of skeletal tuberculosis. For the last four years in this Colony tuberculosis of the spine has been treated by approaching the spine and removing from the affected area all the diseased tissue possible. The resulting cavity is packed with bone chips and streptomycin powder and the wound is closed without drainage. The patient has antibiotic treatment and rest on a plaster bed for four months and then is discharged from hospital in a plaster jacket. This he keeps for what remains of a 12-month period from the time of his operation and is given domiciliary antituberculous drugs: supervision is undertaken at his home and periodic reviews are done at the sanatorium.

The results have been gratifying—no sinuses, no relapses, and only four months' bed-occupancy instead of 24 months with conservative treatment. The time factor was the real driving force, because it meant that we could treat more patients, but in the event their spines were better consolidated. So far, but the days are early, none of the operated spines has reiapsed, but some of those treated without surgery certainly have. Even with our small numbers we have felt the value of the shorter time in hospital and the absence of relapse brought about by adding surgical to antibiotic and constitutional treatment.—I am, etc.,

Suva, Fiji. R. I. COHEN.

Efficacy of Psycho-analysis

SIR,—In depreciating the value of conditioning methods such as employed by Dr. H. L. Freeman and Mr. D. C. Kendrick (August 13, p. 497) to overcome a woman's phobia for cats Dr. Edward Glover (August 27, p. 671) bases himself entirely on a belief that recoveries from neurotic suffering are likely to be inferior in quality or thoroughness if procured without psycho-analytic therapy. The inferiority is taken to be a logical consequence of the proposition that "the patient is left with his or her mental conflicts intact."

Leaving aside the scientific inadmissibility[1] of the "evidence" upon which this and other psycho-analytic propositions are based, let us consider in what concrete way non-analytic recoveries are supposed to fall short. The usual allegation is that in patients apparently cured by non-analytic means the symptoms tend to recur or be replaced by other symptoms (because of the continued presence of "unconscious conflicts"). No statistical evidence has been advanced to support this. On the contrary a recent survey[2] of follow-up studies of non-analytic recoveries has shown only four relapses among 278 patients. Freud's own testimony[3] suggests that the long-term prognosis for psycho-analysed patients is probably no better, to say the least.

Dr. Glover claims to have shown[4] that the conditioning therapy of neurosis described in my book[5] really has its effects only because of suggestion. In a rejoinder[6] to Dr. Glover I pointed out that neurotic behaviour is learned behaviour, that experimental neuroses are overcome by learning techniques to which the derivative reciprocal inhibition methods of treating human neuroses are clearly parallel, and that the results have been superior to those obtained by standard methods of suggestion (or by psycho-analysis). While rigorous statistical studies are certainly indicated, the facts at hand should at the very least have raised in Dr. Glover's mind a doubt about the correctness of dismissing conditioning therapy as another variant of suggestion. However, it is all too convenient that "everything awkward in the field of psychology can be labelled 'suggestion,'" as Freud[7] once remarked. —I am, etc.,

School of Medicine, University of Virginia, Charlottesville, U.S.A. JOSEPH WOLPE.

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Complications of Immunization

SIR,—In comment on the paper by Dr. Justus Ström (October 22, p. 1184), your correspondent Dr. Jill N. Gordon (November 12, p. 1453) refers to neurological complications after poliomyelitis vaccination. In a recent paper entitled "Poliomyelitis-like Illnesses after Polio-vaccination,"[1] Dr. I. B. R. Duncan and I listed three cases whose symptoms developed within 28 days after immunization. Two of these children were paralysed, and one of them died. From all three were isolated strains of Coxsackie A7 virus. This virus was causing an outbreak of paralytic and non-paralytic poliomyelitis-like disease at the time, and I consider that the association between the illnesses and recent vaccination was purely coincidental. The nature of these infections would not have been revealed by conventional tissue-culture techniques alone; inoculation of suckling mice was necessary to demonstrate the presence of Coxsackie A7 viruses.—I am, etc.,

Department of Virology, University of Glasgow. N. R. GRIST.

REFERENCE

[1] Grist, N. R., and Duncan, I. B. R., *Hlth Bull. (Edinb.)*, 1960, **18**, 37.

SIR,—The letters on this subject by Drs. B. D. Bower and P. M. Jeavons, and that of Dr. Jill N. Gordon (November 12, p. 1453) give one food for thought. When one realizes the rarity of any grave sequelae of diphtheria–pertussis immunization or prophylaxis against poliomyelitis, it is obvious that the determining factor is a diathesis in the few subjects which are affected. Clearly this must be so, as thousands of children will be found to have been inoculated with the same batch of material without untoward effects. It is an unfortunate fact that pertussis vaccine is one of the most impure substances which are commonly injected into the human organism, and that attempts to diminish its toxicity seem to be accompanied by loss of antigenic properties; but efforts to produce active pertussis vaccine in purer form continue. Probably poliomyelitis vaccine may be similarly improved in the course of time.

The purpose of this letter is to suggest that perhaps the profession is not doing all that it can to avoid even the commoner complications of immunization. The personal or family history which is obtained before injecting an infant with pertussis vaccine, or combined or triple antigen, is often negligible or deplorably sketchy. If a family or personal history of asthma or eczema in a child is not identified, or is ignored, we know that these conditions can be aggravated or precipitated. The pertussis element should never have been injected. A small trial dose of the vaccine in such cases is, of course, futile: it may merely serve as the sensitizing agent. Carrying this argument a stage further, it appears likely that some of the rare cerebral complications might be avoided if the cases to be inoculated were more carefully selected.

Probably the minimal safe inquiry which should be made prior to the use of pertussis vaccine is as follows: "Baby has always been healthy? Has never suffered from fits or convulsions, asthma, or eczema? Has not been ill or in contact with any disease in the last few weeks? And there is no asthma, eczema, hay-fever, or fits in the family?" This has to be said at a rate which gives the parent time to absorb the questions and to answer them intelligently, and the answers must be carefully weighed up before proceeding with the treatment. The above is my own routine procedure. It would not be popular with those who aim at a sausage-machine type of immunization, where the sole object seems to be to inoculate the largest number of infants in the shortest possible time.

I should be loath to see pertussis, or triple immunization against diphtheria, pertussis, and tetanus, brought into unnecessary disrepute, or to consider the abandonment of pertussis prophylaxis, which I have proved, over the years, to greatly modify the severity of the complaint, and often to prevent it. What I do fervently desire is that medical men should feel a much greater sense of responsibility in the use of the vaccine. This applies to a somewhat less extent in the case of poliomyelitis vaccine. If extra care were universally taken, the less severe complications of pertussis immunization would undoubtedly be reduced in number, and I believe that even the serious rare sequelae might be lessened.

In conclusion, I would like to support Dr. Ian Taylor's view of the value of retaining personal immunization record cards (November 5, p. 1384). The reason why so many of these are lost, or are not produced at the proper time, is that not enough care is taken by the clinic doctor or nurse to see that the parent understands the value of the document, the necessity of keeping it safely, and of bringing it with the child on every attendance at any immunization or vaccination clinic. The value of tetanus prophylaxis is being largely lost by this casual treatment of the procedure. Unless a doctor or hospital knows that a child has been actively immunized against tetanus, together with the dates, prophylactic serum will be given, often (alas) repeatedly, for a number of minor wounds. Why do we bother to inoculate with tetanus toxoid? Not to protect the child against a rare disease so much as to provide a shield against the sharp lance of the serum syringe in hospital.

When immunization is finished, the following remarks are made in my clinics when the mother is handed the record card or certificate: "You see, mother, that this card is stamped TETANUS (in *red*). If you ever take your child to hospital or the doctor with a wound or an accident, always show this card, as it helps with the treatment. Keep it in a safe place, and see that your husband understands about this as well." If you think what you are trying to do when you deal with parents and children, and say what has to be said to make them understand all that is necessary, you will be a slower worker. I am content to be slow.—I am, etc.,

Broadbridge Heath, Sussex. GUY BOUSFIELD.

Doctors' Letters

SIR,—Dr. W. D. Pyle's letter (November 5, p. 1384) is of twofold value. First he suggests a way in which military procedure might improve civilian practice, which I always welcome, and second he recommends a method by which a gentle reproof might be administered to those general practitioners who so grossly misuse the ever-present and ever-ready kindness and courtesy of their specialist colleagues in hospitals.—I am, etc.,

Richmond, Yorkshire. C. ILIFFE.

SIR,—I quite agree with Mr. D. G. Wilson Clyne (October 1, p. 1020) about the danger of the old patient becoming the "chronic old patient," and he very aptly points out the remedy—review. But with due deference it seems open to question that a patient who is found to have a condition belonging to another specialty should not have the benefit of direct referral to the appropriate unit. This need not result in a round of special investigations, and should but result in a letter from the

appropriate consultant to the G.P., who can then give suitable advice with minimal delay. Perhaps I misunderstand Mr. Wilson Clyne, but the time and anxiety involved in hospital consultation are of some moment to the patient and ought to be reduced if reasonably possible. I wonder what the G.P. thinks ?—I am, etc.,

EDWARD PINK.

Department of Obstetrics and Gynaecology,
General Hospital,
Johore Bahru, Malaya.

Dental Hygiene

SIR,—After reading much correspondence and reports of discussions on the question of dental hygiene—I have found it extremely difficult to discover what the dental profession really does think is the correct routine method. Having thought over the question for many years I have come to certain conclusions: (1) that the toothbrush is the most septic object in the bathroom. I am quite sure a culture from most of them would produce horrifying results. It is also nearly always used with a vigorous up and down movement which scarifies the gum margin and injects bacteria between gum and tooth. It should, I imagine, only be used for the biting surface, if it is used at all. (2) That toothpastes are useless and a waste of money. (3) That the only reasonable method is to use interdental sticks after breakfast and before retiring, and then rinse the mouth vigorously with water to force it through the gaps. This is the one employed by primitive people, and because our teeth are closer together it is even more important to keep the spaces clear. It is a very simple method and any child would understand how to do it. I am told that in some Continental countries a child does not leave the table until he has correctly used his toothpick.—I am, etc.,

London W.1. O. GAYER MORGAN.

First-aid for Burns

SIR,—I was interested in your annotation on the first-aid treatment of burns (November 5, p. 1375), in which comment was made on the value of cold as a first-aid measure. The consequences of first- and second-degree burns of the tissues are thought to be brought about by the local production of histamine. This causes local vasodilatation, and a consequent transudation of plasma into the interstitial spaces, causing oedema ; and this, being superficial in the case of burns, may cause blistering. Blisters and their sequelae of fluid loss and sepsis are preventable complications of burns.

Once when I was in a patient's house, she burnt her hand and fingers on a hot grilling pan, which she absentmindedly lifted out of the roasting oven with a bare hand. I immediately applied firm cold-water bandages, which were kept wet. Two hours later, there were no blisters and there was no red reaction. Cold-water bandages were continued until next day, when there was no evidence of the burn, and no further treatment was required. I have frequently repeated this technique, and cases seen soon after burning, before the formation of blisters, have not subsequently blistered. I have instructed patients in this technique, which many have themselves carried out successfully.

The application of cold will tend to produce vasoconstriction, and so counteract the histamine reaction of vasodilatation and the consequent transudation of plasma and formation of blisters—the application of firm pressure also prevents the accumulation of oedema and formation of blisters. Any histamine that is formed is prevented from accumulating locally in oedema, and gets carried away in the circulation, where it is harmless.

This treatment was obviously of limited value in that it could only be applied effectively to burns of limbs and digits which could be compressed, but not to burns of the trunk or face. With the advent of hydrocortisone, it occurred to me that we had a means of preventing the histamine reaction in other parts of the body which had previously been inaccessible to treatment by cold and pressure, since hydrocortisone is a powerful inhibitor of the histamine reaction.

I saw a child who had just been scalded. There was a brilliant erythema over about one-quarter of the trunk, and a few blisters were appearing. Having excised the blisters, I rubbed hydrocortisone and neomycin ointment thoroughly into the burnt area, including the raw surface of the excised blisters, and told the mother to rub it in again three or four times, at half-hourly intervals. Neomycin was used, in addition to hydrocortisone, in view of the risk of infection of the raw surfaces. Twenty-four hours later the erythema had entirely disappeared, no new blisters had lifted, and the ones I had excised were dry. The child required no further treatment.

I now always use hydrocortisone first, and apply cold and pressure as well so far as possible. I use neomycin with hydrocortisone where blisters are already present. The histamine reaction does not develop instantaneously after burning, but takes time, during which it is possible to anticipate and inhibit it. This interval is of vital significance, as it affords an opportunity for preventing the consequences of first- and second-degree burns after they have been sustained.—I am, etc.,

Guildford. ALLEN J. WHITAKER.

Eleven Vaginal Deliveries after Caesarean

SIR,—After lower-segment caesarean section for non-recurring indications it is now common practice to allow a vaginal delivery in the next labour if conditions are favourable. The imponderable factors are the strength of the uterine scar and the risk of its rupture. If this conservative policy is successful in the second delivery the obstetrician must then decide how many more vaginal deliveries should be attempted. The literature on this subject is summarized by Riva and Breen,[1] but nowhere is the answer to this particular problem given. The usual management is to revert to caesarean delivery after two vaginal deliveries on the grounds that the uterine scar must become progressively weaker with the distension of successive pregnancies and labours. Whether this is a valid assumption has never been proved. The case reported here gives ground for belief that if the scar is initially sound it can resist indefinitely the alleged disadvantages of subsequent child-bearing. After 11 vaginal deliveries the patient's uterine scar showed no dehiscence.

Mrs. C. S., a 37-year-old Maori primipara, had a lower-segment caesarean section for a failed trial of labour in 1943, when she was aged 20. The weight of the baby is not known, nor can any information be obtained about the operation or the puerperium. After this she had 11 normal vaginal deliveries during the years 1945–58, the weights of the babies ranging from 6 lb. 2 oz. (2.78 kg.) to 10 lb. 2 oz. (4.6 kg.).

On April 5, 1960, in her thirteenth pregnancy, she had a lower-segment caesarean section and tubal ligation, the indications being mainly multiparity and an anxiety state. No sign of the previous uterine scar was found except for adherence of the visceral peritoneum to that site.

If intrauterine exploration of the scar immediately post-partum reveals no gross defect it is reasonable to advise a vaginal delivery in the next pregnancy instead of reverting to caesarean deliveries on the empirical grounds that two vaginal deliveries should be maximum. This policy would also avoid many of the unhappy late sequelae of repeated caesarean sections which have been pointed out by Dunn[2]—namely, nervous stress, marital disharmony, and arbitrary limitation of family size.—I am, etc.,

Hokianga Hospital, Rawene, New Zealand. E. N. LAMB.

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Myxoedema with Elephantiasis of Eyelids

SIR,—On May 27, 1959, a woman aged 64 was examined in the ophthalmic department. She complained of watering of both eyes and inability to look downwards because of gross swelling of the lower lids (Fig. 1). The puncta were found to be everted but the lacrimal ducts were patent. She was referred to the medical department, where she gave a history of gaining weight for four years and occasional loss of her voice. She had been losing hair, had little energy, and felt the cold. She thought these symptoms had started soon after the death of her husband. In addition to the abnormalities shown in the photograph, she had some swelling of both legs, without pitting. She was slow in her movements and her voice was unusually deep.

FIG. 1

Investigations.—Blood cholesterol was a little raised to 233 mg./100 ml. Her haemoglobin was 80%, otherwise nothing significant was found. The B.M.R. could not be done as she could not retain the mouthpiece. Her weight was 10 st. 10 lb. (68 kg.). In June, 1960, when she had been under treatment for more than 12 months, the weight was 9 st. 12½ lb. (62.9 kg.) and her blood cholesterol had fallen to 160 mg./100 ml.

FIG. 2

FIG. 3

Treatment.—Thyroid extract gr. ¼, gradually increasing to gr. 1, three times a day, later reduced to gr. 1 twice daily. Fig. 2 shows the appearance after six weeks' treatment and Fig. 3 after 18 months' treatment.

Swelling of the lids sometimes associated with watering of the eyes has long been recognized as a sign of myxoedema, but such gross swelling, sufficient to obstruct the vision and justifying the name of elephantiasis, must be unusual. It is interesting to note the almost complete recovery under medical treatment and without surgical intervention.

We are indebted to Mr. R. Marshall, F.R.P.S., of the photographic department of the Cardiff Royal Infirmary, for permission to publish Figs. 2 and 3.

—We are, etc.,

G. WISHART HOARE.
B. GUPTA.

Caerphilly Hospital, Glamorgan.

Philosophy of Beating

SIR,—Having regularly beaten my two male offspring, aged 4 and 7, since the age of 3, in my simplicity I had assumed that this was entirely normal practice, but the apparent need for its defence in a psychiatric context seems to be suggested in Mr. A. W. Fowler's letter "School Phobia" (November 12, p. 1456).

Treatment is administered with whatever weapon is to hand, an unrolled copy of the *B.M.J.* is excellent; the Sunday heavies, and the *Daily Mail* in its new form, are not to be despised; whilst a belt or one's own braces are useful, if one's trousers are sufficiently self-supporting. Loud shrieks and boo-hoos are an essential reaction and results of treatment are usually apparent within half an hour; a more prolonged long-term benefit is the obviously increased sense of security manifested by the patients, who have their guiding beacons of what is not permitted, and their certain knowledge of the wide territory between, in which uninhibited activity is approved.

I have not so far had to carry out a ritual beating, the benefits of which are arguable. Childish "fibbing," for instance, detected after the commission of the offence, is made the subject of a warning that the usual treatment will follow if it occurs again.

I still remain convinced that the large majority of parents behave as I do, but our psychiatric colleagues might profitably consider, and indicate, what types of parents and children are suited to this therapy, as their reputation will be greatly enhanced and gratitude from parents assured. It might indeed lessen their work in other spheres.—I am, etc.,

London S.W.1. ROBERT CUTLER.

School Phobia

SIR,—I was most interested to read in the *Sunday Dispatch* of November 6 that 30 children had been treated for this dread disease by the oral administration of tranquillizers. In my own family the disease is hereditary: both my own son and myself have suffered from it when young. The tranquillizers were in those days administered cutaneously at the other end of the alimentary canal instead of orally, and were not ineffective.

The only trouble with phobias is that, as you cure one, another is liable to take its place. In my case I am getting a phobia against modern medicine. It is probably a case of "everybody is out of step excepting our Johnny!"—I am, etc.,

Newton Abbot, Devon. JOHN V. MAINPRISE.

SIR,—What a pleasure to find a member of our profession emphasizing one of the facts of life. I refer to Mr. A. W. Fowler's letter (November 12, p. 1456). All human beings are only controlled by "reasonable" fear of consequences, preferably tempered with a little love. There seems to be an idea prevailing that we are now dealing with a totally different species requiring a different attitude to their upbringing. The result of this is plain to see. I would suggest that copies of Mr. Fowler's letter should be distributed to all (1) psychiatrists, (2) educationalists, and (3) parents.—I am, etc.,

London E.12. M. C. STARK.

Faecal Incontinence in Children

SIR,—I read Dr. H. Pratap's letter (November 12, p. 1452) with the sinking heart of the parent who has tried all too often to "win" battles with antagonistic offspring, instead of remembering that no one can do this with impunity. It is too easy a way out. Does Dr. Pratap really believe that making a 13-year-old wash his own pants will improve relations between youth and age? Walking about in dirty pants must be nearly as unpleasant as washing them. All right, they are clean now, but what will be dirty next? And why?—I am, etc.,

London W.1. BARBARA EVANS.

Bastard Dosage

SIR,—I was rather surprised to find a new phrase coined in medicine when I read of "bastard dosage" (October 22, p. 1236). This obviously referred to the dosage of aspirin expressed in milligrams per pound of body weight. However, one could trace the origin of the so-called third system to the joint venture of the English (with the apothecary system) and the Americans (with the metric system) and the obvious bastard nature of the origin of the same. This can be avoided easily if only the English doctors would stick to the universal metric system, at least when they undertake a joint international venture.—I am, etc.,

Edinburgh 3. S. K. SEN.

Christmas Gifts Fund

SIR,—I should like to remind your readers who have not yet responded to the Chairman's appeal (October 15, p. 1156) that it is our custom to distribute the gifts some days before Christmas. I hope all who can will send their contributions marked "Christmas Gifts" to the Royal Medical Benevolent Fund, 37 St. George's Road, Wimbledon, London S.W.19, as soon as possible.—I am, etc.,

GEOFFREY H. BATEMAN,
Honorary Treasurer,
Royal Medical Benevolent Fund.

POINTS FROM LETTERS

Sexual Murderers

Dr. W. RUTLAND HILL (Leeds 8) writes: In your issue of October 29 (p. 1304) Dr. A. H. Williams, in speaking of the psychopathology of sexual murderers, is reported to have remarked on (i) the repetitive tendency of such murderers and (ii) their being less amenable to rehabilitative measures. . . . I suggest that "reorientation" or possibly "reclamation" would be more suitable terms to apply to the treatment of these people, but "rehabilitation," no!

Obituary

J. BURNETT RAE, M.B., Ch.B.

With the death of Dr. J. Burnett Rae at Eastbourne on October 31 at the age of 80 psychiatry loses one more of those pioneers who introduced psychological methods for the treatment of "shell shock" during the first world war.

James Burnett Rae was born at Edinburgh on February 6, 1880, the son of John Rae, J.P., of Aberdeen. He was educated at the Aberdeen Grammar School and University, where he graduated M.B., Ch.B., with honours, in 1902. After a short period in practice he was so impressed with the prevalence of spiritual and emotional problems among his patients that he returned to the university as a theological student, and after completing the course served for three years, from 1908 to 1911, as assistant minister at Sefton Park Presbyterian Church, Liverpool. Again he was not completely satisfied with the contribution he was making, and in 1912 he returned to the medical fold. House appointments in general medicine, surgery, and obstetrics were followed by a period of general practice in Yorkshire and in London, where he took the opportunity of developing his natural gift as a hypnotherapist.

During the first world war, while he was serving in the R.A.M.C., his skill as a medical psychologist was soon recognized, and in 1916 he was appointed medical officer in charge of the psychotherapeutic department at the Cambridge Hospital, Aldershot, and a year later he was transferred to the Queen Alexandra Military Hospital, Millbank, as consulting physician in psychological medicine.

After the war he held appointments on the honorary staff at the British Hospital for Mental and Nervous Disorders and the Croydon General Hospital, and was engaged in private practice until 1957, when he moved to Eastbourne, continuing to see occasional patients until he was seized twelve months ago with the illness which proved fatal.

Perhaps his greatest contribution has been his effort to bring religion and medicine closer together, a task for which, in view of his dual qualifications, he was eminently well qualified. For many years he served as vice-chairman of the Churches' Council of Healing, and his election, five days before his death, as first vice-president of the Council gave him particular pleasure and may be regarded as the crowning achievement of his career.

Burnett Rae was a man of great personality and charm, and few doctors can have inspired more affection and loyalty in their patients. He is survived by his second wife and by two sons and a daughter of his first marriage.—T. P. R.

JAMES TAYLOR, O.B.E., M.B., Ch.B., D.P.H. D.T.M.&H.

Dr. James Taylor, who was an assistant county medical officer under the Durham County Council and medical officer of health of Blaydon-on-Tyne, Whickham, and Ryton Urban Districts, died while on holiday in Scotland on September 22. He was 54 years of age.

James Taylor was born in Aberdeen and educated at Bellahouston Academy, Glasgow, and Glasgow University, graduating M.B., Ch.B. in 1929. After holding the posts of house-surgeon at the Glasgow Royal Infirmary and later at the Dumfries and Galloway Infirmary, he joined the Union Castle Line as a ship surgeon and travelled extensively. After leaving the sea he took the D.T.M.&H. of London and then did a short tour for the Colonial Medical Service in Northern Rhodesia. On returning to the United Kingdom he went into private practice in Burnopfield, Co. Durham. He married in 1935, and in 1937 moved to London in order to take the D.P.H. In 1938 he rejoined the Colonial Medical Service and was posted to

Fiji. He will be remembered for his achievements in public health in the Lautoka, Mba, and Nadroga areas of Fiji. He was appointed medical officer of health of Suva in 1945. In 1951 he was transferred to Seychelles as Director of Medical Services. For his outstanding work in public health in this colony he was appointed O.B.E. In 1954 he retired from the Colonial Medical Service, and in 1955 took up the local government appointments which he held up to the time of his death.

He is survived by his widow and two children, to whom we offer our sincere sympathy.

H. S. FABER, M.D.

Dr. H. S. Faber, who was in general practice in Cricklewood for 52 years, died suddenly at his home there at the age of 82.

Hamilton Stanley Faber was born in Stockton-on-Tees on April 19, 1878. He was educated at Uppingham School and St. George's Hospital, where he won the prize in physiology and where he was a member of the lawn tennis team. On qualifying in 1902 he was appointed house-physician to Sir Humphry Rolleston and later house-surgeon to Sir George Turner: he was "on the house" for two years. On leaving the hospital he joined the P. and O. and was a ship surgeon for four years, his last ship being the cruising yacht *Vectis*, in which he travelled to many parts of the world. Having graduated M.D. at Brussels in 1907, he settled down in the following year to general practice in Cricklewood, where he was active up to the time of his death. In the early days he was one of the first motorists and did his rounds in a "metallurgique." He helped run the Willesden General Hospital when it was the Passmore Edwards Cottage Hospital and latterly was its honorary consulting medical officer. Throughout the second world war he served on the medical boards. He was also medical officer to the Midland Railway.

D. H. R. writes: Dr. Faber was a very able physician who upheld the highest traditions of medicine and was a true family doctor. A distinguished and kindly man, he was loved and respected by his patients and colleagues alike. He had a great sense of humour and his outlook was always that of a young man. He was very well read and kept abreast of all the latest developments in medicine. A humorous after-dinner speaker with a dry wit, he kept his listeners very well entertained. I feel that it was a privilege and an honour to have been his partner during the last three years of his life, for during that time we became great friends as well as colleagues.

He leaves a widow and two sons, one of whom will shortly be going up to St. George's to follow in his father's footsteps. To them we extend our sympathy in their great loss.

Sir GORDON GORDON-TAYLOR, K.B.E., C.B. M.D., Hon.LL.D., Hon.Sc.D., M.S., F.R.C.S.

The obituary of Sir Gordon Gordon-Taylor was published in the *Journal* of September 10 (p. 807).

Professor M. A. PAUL has sent us this tribute on behalf of the medical profession in Ceylon: The passing of Sir Gordon Gordon-Taylor leaves us in Ceylon with a deep sense of personal loss. Our tribute to his memory bears witness to the greatness of a man who strove all his life to extend the high standards which came so naturally to him to all men who had the will to work for these standards. Coming to Colombo on several occasions to examine in the Primary F.R.C.S., Sir Gordon captured our imagination with his fine presence, his sincerity of purpose, his skill as a surgeon, and the eloquent orations he delivered at our medical association. This grand ambassador of English surgery soon won our hearts by his affection and interest in us. He kept his personal contact with us, and his Christmas cards, written with his own bold hand, were treasured by us. The last batch of these cards came to us this week bearing a picture of the cricket ground at Lord's with a note on the envelope written by his secretary, Mr. Johnson, informing us that Sir Gordon had died in a road accident.

In 1949, while on leave in England, I was introduced to Sir Gordon, who asked me what I would wish him to do for me. I replied that I did not think it possible, but I would have liked to see him do an interinnomino-abdominal disarticulation. Before I left England I was invited three times to the Middlesex Hospital to witness this surgical feat performed by a master surgeon who had retired from active surgery some years before. At these operations one could not help noticing the affection of all at the Middlesex for their great chief. In those days it was the practice of students and teachers working at the Royal College of Surgeons to repair into the basement for lunch and a little respite from hard work. At these lunches I have seen Sir Gordon introduce himself to a lonely student from overseas to have lunch with him and cheer him up. Sir Gordon was a giant of the surgical world—so gentle was this giant with the humblest of his surgical tribe. We loved him. We shall miss him.

Sir HAROLD GILLIES, C.B.E., F.R.C.S.

The obituary of Sir Harold Gillies was published in the *Journal* of September 17 (p. 866).

Mr. THEODORE PHILLIPS writes from Philadelphia: I was the publisher's editor at Little, Brown and Company in Boston of Gillies and Millard's *The Art and Principles of Plastic Surgery*. You may be interested in some personal recollections concerned with the production of that extraordinary book. The express company brought in two odd-shaped leather valises addressed to me. The contents were Gillies's manuscript—a huge conglomeration of typed and handwritten manuscript and some 3,500 black-and-white illustrations, all in great disorder. Being only an editor, I am unfamiliar with the Bentley motor-car. It was a year later before I knew that these containers are designed to fit the luggage compartment of this car, and later Gillies told me the Bentley was his most prized possession and that he had sold it to pay some of the costs of preparing his manuscript.

There followed two exciting years with masses of correspondence between Boston and London with many embellished inked sketches expressing his pleasure, or more frequently his displeasure. His letters were pungent and full of puckish humour. He was emphatic in his demands, and often unreasonable, but only his bark was ferocious, not his bite. He damned me to high heaven and more than once wrote to throw the manuscript in the waste basket. The next mail would bring his retraction and forgiveness for my stupidity.

He insisted that none of the illustrations be numbered and that the pages be so set that one saw as one read. As Mr. Rainsford Mowlem expressed it in your journal, he was "completely untrammelled by any preconceived ideas as to how things 'should be done.'" This created a copy-editing and composition nightmare. Eventually my presence was required in London. There followed ten hectic days at 149 Harley Street. His extraordinary book was finally published and successfully sold. I believe no other book quite like it has appeared in medical literature. The proudest moment in my editorial career was when I sent him his first royalty cheque: it was substantial even by American standards and justly deserved. He was truly a most lovable genius whose passing will be mourned most grievously by the thousands of men and women who walk in life unscarred owing to his skill.

MAX LOEWENTHAL, M.D., M.R.C.P.

The obituary of Dr. Max Loewenthal was published in the *Journal* of October 22 (p. 1243).

The following tribute has been received from a correspondent in South Africa: Max Loewenthal was an example of the thorough education provided in the last

century. He studied medicine at Berlin and Würzburg, passing out with what to-day would be termed "honours" in all subjects, and his subsequent standard of excellence was undoubtedly due to the teaching which he received from such outstanding lecturers as DuBois Reymond, Helmholtz, Virchow, and Leube. It was small wonder that he was admitted a Member of the Royal College of Physicians within a few months of his arrival in London in 1894. After he had moved to Liverpool he soon became recognized as a general practitioner of outstanding merit, and he practised there uninterruptedly until his retirement in 1935. His name is still familiar to many of his old patients as well as to their children and grandchildren, some of whom would visit him in Johannesburg after his retirement.

Max Loewenthal's interests were wider than those associated with the conduct of a medical practice, and he published articles in the field of physics, and completed many years of careful thought with his work *Life and Soul*, published in 1934. This was a theoretical exposition of the nature of life based on original physiological and philosophical concepts, and was well received by those whose interests were not limited to mere material considerations. His mental gifts were outstanding and his memory for even recent events surprisingly preserved until the end. His recollections of early days, including the French prisoners who were quartered in his town during the Franco-Prussian War, were fascinating. He would recount anecdotes of the Napoleonic Wars told to him by his grandmother during his childhood. Chess was his favourite relaxation, and he was a player of outstanding merit, having known many famous masters such as Lasker and Steinitz personally and having played against them. At the age of 86 he played first board for Natal in the South African Provincial Tournament and won all his games. His love of the classics was preserved, and even in his last years he made passable translations of some of Horace's Odes into English and would often cap a Latin quotation. He left numerous papers on such diverse subjects as physics, botany, and philosophy, which may be published posthumously.

Medico-Legal

NEGLIGENT DIAGNOSIS

[FROM OUR LEGAL CORRESPONDENT]

On October 28, in the Southampton County Court, Judge J. C. D. Harington, Q.C., awarded damages of £115 against Dr. L. B. D'Arcy, a general practitioner, who was sued for negligence in respect of a month-old baby (*Daily Telegraph*, October 29). The action was brought by the 22-year-old father of the baby, Mr. L. W. Riddett, of Nelson Street, Southampton.

Mr. Riddett gave evidence that on Sunday, January 18, he called Dr. D'Arcy to see his baby. At that time, said Mr. Riddett, the baby was icy cold, displaying a mauve colour and swelling about the eyes, and was breathing irregularly. According to Mr. Riddett, Dr. D'Arcy said, "He is cold, isn't he? A dose of castor oil will do him good and bring up the wind." The next day, said Mr. Riddett, he made certain 'phone calls, and in the evening Dr. Nally (a partner of Dr. D'Arcy) called and saw the baby. Dr. Nally at once sent for an ambulance, but the child died in hospital of a staphylococcal pneumonia.

A Fulminating Infection

Dr. D'Arcy's case was that when he saw the baby he examined the child's ears and chest and took its temperature. The heart, temperature, legs, and hands were normal, and the baby was not icy cold. All that was discernible was a runny nose. He diagnosed that the child had a cold.

According to the medical evidence, the baby's illness could have been a fulminating infection and have become critical in a matter of six hours. The onset of this type of pneumonia was variable: but, if the parents' description was correct, the baby was sick on the Sunday, and this should have been apparent to a general practitioner. Evidence was given by Dr. J. R. Burwell and Dr. A. Doyne Bell for the plaintiff, and by Dr. C. Bartley and Dr. J. H. Moseley for the defence. The central issue before the judge was simply whether, this being a fulminating infection, the prodromal period had ended and the symptoms of heart failure had become apparent enough to be observed by a reasonably skilled doctor at the time of Dr. D'Arcy's visit. The judge found on the evidence that symptoms of heart failure were present and that Dr. D'Arcy's examination was insufficiently close to enable him to notice the symptoms. On that finding, he held Dr. D'Arcy to have been negligent.

It should be added that the judge emphasized that there had been no suggestion whatever against Dr. D'Arcy in the normal conduct of his practice. There was no suggestion that he was usually anything but the normal careful doctor. However, on this one evening, in the judge's view, he had been negligent in his examination.

The £115 damages included a claim for funeral expenses. In accordance with the normal practice, the amount awarded for loss of expectation of life of a small baby was small. Since the hazards of life are greater for a baby or young child than for a young adult, and since it cannot be confidently said that the baby or child could have anticipated a happy life, the damages for loss of expectation of life in such case must necessarily be small.

Medical Notes in Parliament

PUBLIC HEALTH BILL

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The Public Health Bill, which was introduced in the House of Lords on November 10, seeks to incorporate into the general law a number of statutory provisions which the experience of local authorities has shown to be necessary and which are for the most part already included in local Acts. The Bill was due to receive its second reading on Thursday, after we have gone to press.

Notification of Disease

Among the more important of these extensions are the clauses relating to the prevention and notification of disease. Clause 34 provides that a justice of the peace may order the medical examination of any person if he is satisfied, on a written certificate from the medical officer of health, that the person was or had been suffering from a notifiable disease, and that such an examination was expedient in the public interest or the interest of the person concerned or his family. Clause 35 requires the occupier of premises in which there is or has been someone suffering from a notifiable disease or food-poisoning to furnish the medical officer of health with such information as he may reasonably require to prevent the spread of disease or trace the source of food-poisoning. As a further measure to prevent the spread of a notifiable disease, Clause 36 enables a local authority, on the advice of the medical officer, to prohibit or restrict the admission of young persons to places of entertainment or assembly.

Building and "Trade Effluents"

New provisions in the Bill replace by centrally made regulations the building by-laws at present made by local authorities. There is to be a building regulations advisory council to advise the Minister in making these regulations.

Part V proposes amendment of the Public Health (Drainage of Trade Premises) Act, 1937, in accordance with the recommendations of the Armer Report published last January. The main effect of the change would be to enable local authorities to make charges (subject to a right of appeal) for the reception into public sewers of certain trade effluents exempted from the 1937 Act. It would classify as trade effluents effluents from farms and from premises used for scientific research; and would also authorize the Minister to remove the special exemption given to laundry effluents in 1937 if their discharge would be likely to cause special difficulties in the treatment or disposal of sewage.

QUESTIONS IN THE COMMONS

Diesel Fumes

Mr. N. DODDS (Erith and Crayford, Lab.) asked the Minister of Health, as representing the Minister for Science, for details of the experiments carried out on behalf of his department which showed that diesel fumes were not endangering health. Mr. ENOCH POWELL stated in reply on November 11 that investigations into the effects on health of diesel exhaust fumes formed part of the programme of research on air pollution undertaken by the Medical Research Council. They had included statistical studies on a large group of patients with lung cancer, which showed that in this group there was no greater proportion of persons who might have been expected from the nature of their employment to have greater exposure to vehicle exhaust fumes; and a study on London Transport employees, in collaboration with the Chief Medical Officer of London Transport, which provided no evidence of significantly greater mortality from lung cancer among men working in diesel-bus garages. Analyses of the air in bus garages and busy streets had shown that motor exhaust fumes were only one of many pollutants and that their content of benzpyrene, a known cancer-producing agent, was very small in relation to the total amount in the atmosphere from all sources. Even in congested spaces such as vehicular tunnels, pollution from exhaust fumes had been found to be no greater than the pollution of an urban atmosphere by coal-smoke on many winter evenings. It seemed reasonable, therefore, to deduce from these findings that diesel fumes were not endangering health.

Protection Against Smog

Dr. ALAN THOMPSON (Dunfermline, Lab.) asked the Minister whether, in view of the abnormally high incidence of chest and heart cases in industrial areas of Great Britain, he will give immediate consideration to measures to protect the health of citizens from the effects of smog in the forthcoming winter. Miss EDITH PITT, Parliamentary Secretary, told him on November 14 that facilities for the care and protection of persons liable to suffer in smog conditions will be available under the Health Service, including provision of special masks. Warning and advice will be broadcast by the B.B.C. when persistent fog was expected.

Progress with Polio Vaccination

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister to state the percentage of children and adults respectively who had now been immunized against poliomyelitis. Mr. POWELL said that, by September 30, 76% of those under 18 and 52% of older persons up to 28 had had at least two doses of poliomyelitis vaccine. These figures did not include any of the 687,000 persons in the special priority groups, not classified by age, who had had two doses.

In reply to a similar question from Mr. J. MCINNES (Glasgow Central, Lab.) on November 15 about Scotland, Mr. T. GALBRAITH, Joint Parliamentary Under-Secretary, Scottish Office, said that the number of people who had been vaccinated against poliomyelitis under the Health Service in Scotland was at September 30 over 1,600,000. This figure included 82% of children born since 1943, and 42% of those born between 1933 and 1942—that is, the adolescents and young adults. Local health authorities, with the help of the Department of Health, were continuing to publicize the facilities they provided for vaccination and the need for persons not yet vaccinated to come forward. Family doctors will also continue to play an active part in encouraging their patients to be vaccinated.

Ministry's Hospital Development Unit

The Minister of Health was questioned by Mr. L. FAVITT (Willesden West, Lab.) on November 14 about the work of the department's hospital development unit. Mr. POWELL informed him that there were 13 full-time and 8 part-time officers in the unit. Its function was to ensure that the most up-to-date knowledge and experience was assembled and brought to bear on all aspects of hospital building. The unit had published already a booklet on operating-theatre suites, and was preparing for publication further bulletins on specific departments, in addition to some 30 building notes on the features and standards which should be embodied in the design of modern hospitals. It would itself be responsible for an out-patient department and kitchen which were to be built as development projects.

Hospital Extensions in Scotland

Miss M. HERBISON (North Lanarkshire, Lab.) asked on November 15 what provision there was in the West of Scotland for the treatment of and research in rheumatological diseases. Mr. GALBRAITH stated that the Regional Hospital Board had decided to add to the existing facilities a new rheumatology unit of about 50 beds. It would be located in Baird Street Hospital, Glasgow, which will be specially adapted for the purpose.

Mr. W. HANNAN (Glasgow, Maryhill, Lab.) drew attention to the high infant mortality rate in Glasgow compared with other Scottish cities, and asked what immediate action will be taken to provide more maternity beds there. Mr. GALBRAITH replied that the regional board expected to open 90 additional beds next year, and were continuing to explore other possibilities of providing additional beds urgently in advance of the completion of the new Yorkhill Maternity Hospital. (A note about infant mortality in Glasgow appears at p. 1610 in this issue.)

Eyesight of Aged Drivers

Mr. CYRIL OSBORNE (Louth, Con.) asked the Minister of Transport on November 16 if, in order to reduce the number of road accidents, he will introduce legislation compelling all drivers over 70 years of age of road vehicles to undergo an annual eyesight test, and to make it conditional that no new driving licence will be issued unless a minimum eyesight standard is reached.

Mr. ERNEST MARPLES stated that at the beginning of every driving test a candidate was asked to read a number-plate at a distance of 25 yards: If he could not do so the test was cancelled. Drivers seeking renewal of their driving licences must declare whether they could read a motor-car number-plate 25 yards away. Licensing authorities refused a licence application or revoked an existing licence if they became aware that a driver's eyesight did not reach that standard. He did not think that further legislation was necessary.

Rebate for Expenditure on Books and Research

Mr. M. WOODNUTT (Isle of Wight, Con.) asked the Chancellor of the Exchequer if he will broaden the scope of Paragraph 7 of the 9th Schedule to the Income Tax Act, 1952, to include expenditure incurred by professional men and women on books and research necessary to keep them up to date in their subject.

Sir EDWARD BOYLE, Financial Secretary to the Treasury, replied that the Chancellor would bear this point in mind, along with the other representations he had received, when he came to prepare his Budget statement.

Dr. H. KING (Southampton, Itchen, Lab.) pointed out that the Royal Commission on the Taxation of Profits and Income had made this recommendation, among others, and

said that the professional classes felt that the Chancellor had dealt unjustly with them in this. Mr. WOODNUTT asked the Financial Secretary to agree at least that the request was reasonable. Sir EDWARD BOYLE: "It is a request which should be considered along with many other requests and points of a rather similar nature."

Group Practice Loans

Mr. L. PAVITT (Willesden, West, Lab.) asked the Minister of Health on Nov. 21 why the average time for approving loans to group practices was four and a half months; and if he would take steps to shorten this period. Mr. POWELL replied that the committee needed this time to study the proposed arrangements and plans, to visit the groups, and to get agreement to any modifications necessary.

Mr. PAVITT said he was aware of the important work being done by the committee, and most general practitioners would agree on the necessity for seeing that group practice was not merely a partnership. He asked the Minister to do what he could to bring the maximum time nearer to the average of 4½ months. Mr. POWELL agreed, but pointed out that part of the time might be spent by the doctors concerned in considering proposals put to them by the committee.

Mr. PAVITT also asked what was the maximum loan granted per doctor in a group practice receiving loans from the fund established for that purpose. Mr. POWELL stated that this was £2,500.

Mr. PAVITT asked him to resist any pressure that might arise to reduce the sum of £2,500 in order that there should be more loans of a lesser quantity. Would he also consult the Chancellor of the Exchequer with a view to raising the amount of money available for this important project? Mr. POWELL said that was the maximum, but the committee had discretion to allow larger sums in particular cases.

Leucotomy Report

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister when he expected to receive the report of the follow-up review being made by his department on cases of leucotomy which was initiated in December, 1955. Mr. POWELL announced that this review had just been completed.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

In Congregation on October 29 the following degrees were conferred:

M.D.—*C. G. Rob, P. C. Gautier-Smith, P. A. J. Ball, D. Wise, J. C. Kelsey, J. H. Cule.
M.B.—T. J. Willis.

In Congregation on November 12 the degree of M.B. was conferred on R. H. C. Vaux.

*By proxy.

UNIVERSITY OF GLASGOW

In Congregation on November 5 the degree of M.D. was conferred on W. Cullen (with commendation) and on J. Sluglett.

UNIVERSITY OF LONDON

Mr. J. B. Hume has been re-elected chairman of the Council for External Students for 1960–1.

The title of Professor of Occupational Health in the University has been conferred on Dr. R. S. F. Schilling in respect of his post at the London School of Hygiene and Tropical Medicine.

The following candidates have been approved at the examination indicated:

THIRD M.B., B.S.—[1 2 4]G. M. Besser, [1 2]D. J. Galton, [1 4]Margaret L. Jones, [1 3 4]H. A. Lee, [1 4]P. H. Millard, [1 3]Jennifer P. Peebles, [1 2]B. A. Senewiratne, R. O. Addae, A. Adeniyi, F. P. Adler, A. Andan, M. F. Anderson, W. C. Anoff, E. N. Armitage, P. M. Ashby, Susan M. Atherton, A. F. J. Atkins, B. N. Ballantune, R. B. Barrett, J. L. Beecher, Audrey J. Belsham, W. H. C. Berry, Margaret L. Birtwistle, R. G. Black, Shirley M. Blackman, P. D. Blade, A. R. H. Bliss, Sonia G. Bolton, Shirley A. Bond, D. Booth, J. G. Bradbrooke, C. L. Bray, W. Brown, M. D. Burgess, Evelyn M. J. Callis, B. J. Camp, H. M. Carpenter, I. P. Cast, Bernard Wan-Bun Chan, J. Chapman, K. G. A. Clark, Jane M. Clegg, N. M. Cole, Heather J. Collins, Pauline T. Combe, D. Corless, Dorothy K. Cory, J. C. Craggs, Jennifer Craig, M. Culloty, J. C. Cummins, D. J. W. Darby, Margaret Davidson, G. Davies, Gillian M. Davies, P. B. M. Davis, R. S. Dawkins, A. D. Dean, J. M. Dinham, P. G. J. Dobson, I. S. Duff, Diana Dutton, J. D. Eddy, D. P. Edmunds, D. A. Edwards, R. W. England, A. W. G. English, P. R. Evans, C. B. Everett, Ann D. Fairclough, H. M. Fisher, D. J. Fishlock, R. A. Forster, J. V. Fowles, Joanna M. Fraser, S. Freedman, Gillian Freeman, S. Freudenberg, Jill Fyfield, Gillian A. Garnett, J. A. Garrod, A. R. Geach, Penelope A. Gething, Sheila M. Girvan, W. A. Gould, Patricia A. Green, Patricia E. L. Greenlaw, J. L. Grogono, Pamela M. Haigh, Joyce C. Hall-Tomkin, Josephine E. Hammond, R. G. Harding, N. F. Harley, R. I. Harrison, J. C. Hasler, J. D. Hatch, I. B. Hayter, J. B. Hicks, G. T. Hollingworth, D. A. Hollis, Alison M. Holloway, P. T. Horder, A. S. Horniblow, E. R. Howard, D. P. M. Howells, D. Hughes, G. V. Hughes, Janet E. Hughes, J. P. Hughes, M. S. Hughes, D. McA. Hunter, Joanna E. Hunter, J. A. Hunter, Pamela J. Hunter, A. C. M. Inwald, R. McK. Jeffery, K. A. Johansen, M. L. Jones, P. A. Jones, Winifred A. Kane, J. H. Kiff, A. W. Kilroy, D. King, D. P. E. Kingsley, K. Kyei-Mensah, T. R. Lawson, D. A. Lee, Sheila J. Lees, T. Lehner, Eveline B. McCulley, R. H. Mackeith, R. F. M. McKenzie, A. C. MacLean, D. R. Macnair, W. J. McNeilly, K. M. A. Madgwick, M. P. Madigan, E. J. B. Makin, B. Malek, Elaine M. Maliphant, E. B. Mama, Deirdre H. Marlow, G. S. Martinez, Bridgett A. Mason, R. J. Mecoy, Joanna Merry, G. M. Michael, Felicity A. Milburn, M. H. Millward, R. D. G. Milner, C. A. L. Moon, J. Moore, R. W. Morris, Ursula V. L. Morris, J. D. Morrison, C. W. Mortimer, P. B. Mudge, F. G. M. Musieh, J. F. O. A. I. Mustaffah, T. G. Nash, H. G. Naylor, M. I. M. Noble, J. R. Norman, Margaret A. Nunan, E. Ojinmah, C. N. Paine, Ann Parker, J. B. R. Parker, Rosemary C. Parrington, Sheila M. Pask, J. P. Patten, J. F. Pearson, J. Pearson, Heather Pell, H. G. Peters, A. H. Pickering, D. A. Pocock, C. J. F. Pool, A. E. Pratt, R. B. Priscott, E. Proctor, V. Promtatvethi, Yvonne F. Ransley, Jacqueline J. Rees, J. H. K. Reeves, D. S. Restall, R. S. Richardson, Anne P. Roberts, J. R. Robson, I. C. Roddick, P. J. Sanderson, T. Sherwood, Ann Simpson, I. P. Slee, D. H. Smith, P. Smith, P. H. Sönksen, C. J. Spivey, D. J. Stern, A. F. S. Stewart, H. J. S. Sudgen, D. R. Sutherland, D. J. M. Taylor, G. W. Thomas, W. H. Thomas, R. G. N. Thomson, Sheila M. Thwaites, Angela R. Till, Isobel Tomkins, F. D. Trevarthen, W. Tsao, P. L. H. Vernon, H. Wagman, C. J. S. Walter, G. G. Ward, R. J. Warner, P. H. Waterfield, A. V. Watkins, C. L. W. Webb, Diana V. A. Whitaker, M. MacK. Wicks, Wendy E. Williams, D. G. Willits, D. P. Winter, Margaret Woodford, Rosemary J. Wool, F. M. Young, Ting Chiu Yu.

[1]With honours. [2]Distinguished in medicine. [3]Distinguished in applied pharmacology and therapeutics. [4]Distinguished in surgery. [5]Distinguished in obstetrics and gynaecology.

UNIVERSITY OF WALES

WELSH NATIONAL SCHOOL OF MEDICINE

The following candidates have satisfied the examiners at the examination indicated:

DIPLOMA IN TUBERCULOSIS AND CHEST DISEASES.—A. Ahmed, J. O. W. Ang'Awa, G. A. Chowdhury, P. G. Dastidar, C. Kulanayagam, M. K. K. Menon, J. T. C. Ramalingam.

UNIVERSITY OF BIRMINGHAM

Dr. R. L. Edwards has been appointed Senior Lecturer and First Assistant in the Department of Obstetrics and Gynaecology.

UNIVERSITY OF BRISTOL

The following appointments are announced: Dr. Gillian M. Churcher, Demonstrator in Bacteriology and Assistant Bacteriologist in the Public Health Laboratory; Dr. P. A. Evans and Dr M. J. Lewis, Demonstrators in Pathology; Dr. G. S. Makin and Dr. A. K. Yates, Demonstrators in Anatomy; Dr. Valerie J. Marrian, Lecturer in Child Health.

The following have resigned from the appointments indicated in parentheses: Dr. J. B. Bowes, Dr. B. Philpott, and Dr. P. J. Roffey (Tutors in Anaesthetics); Dr. Suzanne K. R. Clarke (Lecturer in Bacteriology); Dr. D. J. Sheerboom (Recognized Teacher in Public Health); Dr. K. Simpson (Tutor in Child Health); Dr. B. Woods (Tutor in Dermatology).

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on November 10, with Sir Arthur Porritt, President, in the chair, arrangements were made whereby the professorship of military surgery at the Royal Army Medical College should become a joint professorship with the College.

The programme was drawn up for the annual meeting of Fellows and Members on December 7.

The Hallett Prize was awarded to J. L. Mercer, of St. Thomas's Hospital Medical School, and the Begley Prize to Joseph Brown, of King's College Hospital Medical School.

Diplomas of Membership were granted to the candidates whose names appear in the report of the meeting of the Royal College of Physicians of London held on October 27, printed in the *Journal* of November 19, p. 1532.

A Diploma in Child Health was granted, jointly with the Royal College of Physicians of London, to P. L. Rajbhandari.

After the meeting the second Watson-Jones Lecture was delivered by Dr. Preston A. Wade on "The Accident Surgery of Motorways."

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on November 1, with the President, Dr. A. Rae Gilchrist, in the chair, the following were elected Fellows of the College:

E. James, M. M. Whittet, K. K. Datey, H. G. H. Richards, H. R. L. Fraser, A. B. Hegarty, J. S. Robson, J. A. Loraine, T. S. Row, R. C. Jackson, Velva Schrire, Agnes L. Scott, B. C. Sinclair-Smith, A. C. Kennedy, J. Butler, K. L. Stuart, A. Jarrett, A. R. Somner, D. S. Nand, Sir Samuel L. A. Manuwa, J. H. Hutchison, D. F. Cappell, J. H. Walters, K. W. Donald, A. W. Woodruff, E. Samuel.

The following were elected Members of the College:

C. W. Kidd, A. P. Meiklejohn, R. M. Vanreenen, K. R. Purohit, H. L. Davis, R. W. McConnachie, T. Vamadevan, A. R. Adams, N. R. Young, W. McQuaker, S. O'Reilly, L. H. Harris, D. G. B. Powell, D. Jacobson, Elaine M. Belton, R. Emery, J. K. Binns, S. M. Haneef, R. Singh, G. C. Timbury, J. Gait, B. Lewis, A. M. Sur, R. G. B. Williamson, H. M. El-Sayed, S. M. O. Hilal, M. C. Mathews, A. I. Rae, Frank Tsu-Chang Hu, D. Burrows, N. M. Mathai, B. R. Patel, B. S. David, A. G. Motiwale, P. Taylor, N. P. Burns, K. Hingorani, J. D. Woolridge, Boon-Kheng Khoo, I. R. Lawson, P. N. Krishnamurthy, K. H. A. Mitha, N. K. Channappa, R. A. Osborn, Dona Priyalatha Wijesinghe, M. D. Bowie, L. L. Basta, V. Gupta, E. Lynghdoh, M. G. Dunnigan, I. Michie, H. Ranasinghe, E. E. Eyo, C. J. B. Ram, K. Datta, S. C. Munsi, S. Sen, C. K. Gopi, M. Ata, J. A. Waddell, B. S. G. Singhal, C. Gupta, J. Levin, E. S. Garnett, G. J. Ebrahim, W. H. S. George, J. A. McBride.

A Hill Pattison-Struthers Bursary for 1960 has been awarded to Dr. Philip Lanzkowsky.

The Jean Hunter Prize for 1960 has been awarded to Dr. Andrew William Ernest Soysa.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At the annual meeting of the College, held on October 18, the following officers were elected: *President*, Dr. R. E. Steen; *Registrar*, Dr. Charles Dickson; *Treasurer*, Dr. Geoffrey Bewley; *Representative on General Medical Council*, Dr. Edward T. Freeman.

Dr. P. J. Faul and Dr. G. A. Kernohan have been elected Members of the College.

The Diploma in Obstetrics (Dublin) has been granted to Dr. T. F. Canty and Dr. M. Ahmad-Genaidy.

ROYAL COLLEGE OF SURGEONS IN IRELAND

On November 17 the Fellowship in Surgery of the College was conferred on H. B. Devlin, D. G. Kelly, and W. J. Twibill.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS

At the annual meeting of the Faculty, held on November 7, the following office-bearers were elected: *President*, Dr. J. H. Wright; *Visitor*, Professor C. F. W. Illingworth; *Honorary Secretary*, Dr. Gavin B. Shaw; *Honorary Treasurer*, Mr. R. B. Wright; *Honorary Librarian*, Dr. A. L. Goodall; *Representative on the General Medical Council*, Professor D. F. Cappell; *Representative on the General Dental Council*, Professor W. Malcolm Gibson.

M. A. K. Mansour was admitted a Fellow of Faculty *qua* surgeon.

The Macewen Medal for 1959–60 was awarded to I. W. Young.

QUEEN ELIZABETH THE QUEEN MOTHER will open the new Health Exhibition Centre of the Royal Society of Health on March 1. The Exhibition Centre, which has been designed to display the best current practice in all branches of public health, is said to be the only one of its kind in the world. It will contain sections on: clear air, communicable diseases, drainage and sewerage, food, health and welfare services, lighting, heating and ventilation, occupational health, pest control, public cleansing, radiation, sewage disposal, site planning and building construction, vital statistics, and water.

Vital Statistics

Infant Mortality in Glasgow

In his annual report for 1959 Dr. W. A. HORNE, medical officer of health of Glasgow, states that there is still no sign of any marked reduction in the infant mortality rate in Glasgow. The rate has remained in the neighbourhood of 35 since 1955, and at 35.4 the rate for 1959 is slightly higher than that for 1958. The rate for Scotland as a whole in 1959 was 28, and for England and Wales it was 22. The most prominent causes of infant deaths in Glasgow are the diseases of early infancy, particularly prematurity and congenital malformations. Dr. Horne attributes the outstanding weakness in Glasgow to a deficiency in maternity hospital accommodation. Less than 60% of Glasgow mothers are confined in hospital, and the corporation has continued to make representations to the Government on the extreme urgency of the need for more maternity beds. There was also an increased number of deaths among young children aged 1 to 5—117 in 1959 compared with 86 in 1958. The commonest cause was accident or violence. In an attempt to reduce home accidents at all ages, arrangements have been made for hospitals to report to the medical officer of health all accident cases treated as in-patients or out-patients.

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available

	Week Ending Nov. 5	Week Ending Nov. 12
Measles		
Lancashire	1,700	**1,553**
Burnley C.B.	142	**93**
Liverpool C.B.	259	**200**
Manchester C.B.	130	**90**
Oldham C.B.	167	**176**
Leigh M.B.	104	**99**
Dysentery		
Lincolnshire	6	**30**
Horncastle R.D.	2	**19**
Nottinghamshire	42	**25**
Carlton U.D.	10	**14**
Yorkshire West Riding	71	**90**
Bradford C.B.	4	**24**
Leeds C.B.	39	**41**
Glasgow	101	**122**
Food Poisoning		
Yorkshire West Riding	20	**90**
Settle R.D.	0	**43**

Road Deaths in September

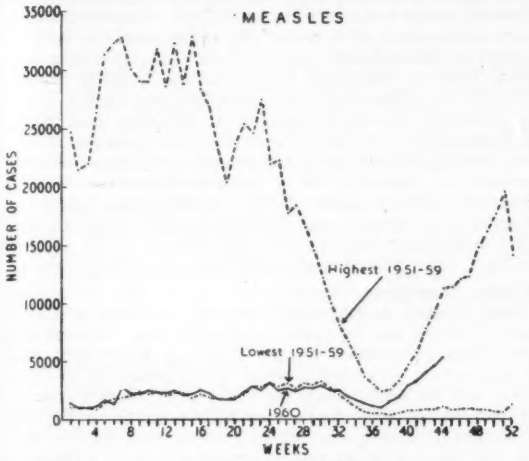
619 people died as a result of road accidents in September, 51 more than in September last year. Most of the increase was due to accidents to pedestrians, 243 of whom were killed (being 40 more than a year ago), including 60 children, an increase of 12. September was the worst month for fatal casualties among child pedestrians for over four years.

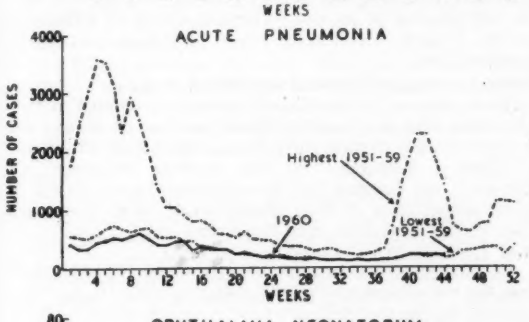
The total number of killed and injured in September was 30,619, an increase of nearly 4% over last year. The volume of motor traffic was 7% higher than in September last year.

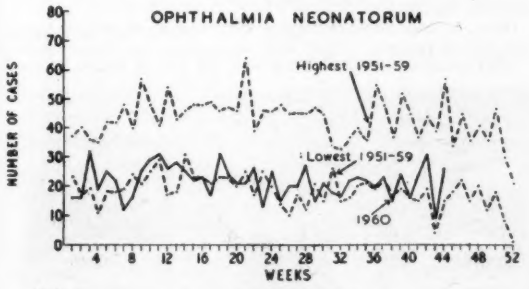
Graphs of Infectious Diseases

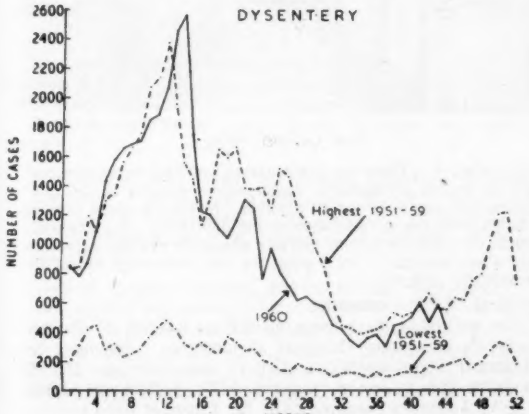
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during

the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **November 5** (No. 44) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria ..	4	0	3	0		3	0	5	0	
Dysentery	422	56	166	9	4	443	45	193	3	1
Encephalitis, acute	3	1		0	1	2	1		0	
Enteric fever:										
Typhoid ..	2	0	0	0		3	1	0	0	9
Paratyphoid ..	2	1	0	0		9	0	0	0	1 (B)
Food-poisoning ..	161	24	15	1		177	36	16	0	
Infective enteritis or diarrhoea under 2 years				16	41				19	31
Measles*	5,280	288	96	15	39	1,196	22	15	0	42
Meningococcal infection	18	0	9	0	1	14	2	6	1	3
Ophthalmia neonatorum	26	3	2	0		18	3	6	0	
Pneumonia† ..	215	21	132	2	1	177	13	111	6	
Poliomyelitis, acute:										
Paralytic ..	8	1	1	1		12	2	0	0	
Non-paralytic ..	2	1	1			2	0	0		
Puerperal fever§ ..	175	29	7	0		199	24	13	2	
Scarlet fever ..	416	23	67	24	25	1,025	48	147	22	36
Tuberculosis:										
Respiratory ..	363	46	68	11		430	41	54	14	
Non-respiratory	56	3	12	3		50	7	13	2	
Whooping-cough ..	1,000	73	86	15	59	568	26	130	5	89

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	4	0	3	7	0	0	0	1
Influenza	15	1	2	0	0	22	1	0	1	1
Measles	0	0	0	0	0		0	0	0	0
Meningococcal infection		0	0				1	0		
Pneumonia ..	459	35	23	14	8		34	19	11	7
Poliomyelitis, acute	0	0		0	0	1	0		0	0
Scarlet fever ..	0	0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	62	1	4	1	2	63	3	5	2	3
Non-respiratory		0	0	0	0		0	0	0	0
Whooping-cough ..	0	0	0	0	0	0	0	1	0	0
Deaths 0–1 year ..	318	37	27	8	12	314	33	28	8	17
Deaths (excluding stillbirths) ..	9,758	776	583	116	157	9,208	779	540	133	154
LIVE BIRTHS ..	14,485	1238	1003	251	351	13,385	1063	897	260	340
STILLBIRTHS ..	289	15	16			248	22	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Glasgow Division's T.V. Programme

The Glasgow Division of the British Medical Association in co-operation with the surgical and orthopaedic departments of the Western Infirmary, Glasgow, presented four medical colour-television programmes on November 8, 9, and 10. The programmes, each of which was attended by about 500 medical practitioners, were relayed from the Western Infirmary to the McLellan Galleries. The technical arrangements were in the hands of Smith Kline and French Laboratories Ltd.

The pattern followed was much the same for each session. A series of patients was demonstrated and the clinical diagnosis discussed. Operative techniques, as well as those of the radiotherapist and the pathologist, were shown. Some of these were live, in other cases judicious use was made of film. Professor C. F. W. ILLINGWORTH acted as moderator for the first session, a symposium on the diagnosis of lumps, with particular reference to lumps of skin, breast, and the thyroid gland. The members of the panel were: Mr. A. P. M. FORREST, Mr. D. H. CLARK, Mr. I. A. MCGREGOR, Dr. W. W. BUCHANAN, Dr. B. LENNOX, Dr. J. R. ANDERSON, and Dr. G. FLATMAN. The panel members for the second session, on transventricular mitral commissurotomy, were: Mr. G. SMITH, Dr. R. L. RICHARDS, Dr. A. J. V. CAMERON, Dr. J. F. BOYD, Dr. S. D. SCOTT PARK, and Dr. A. G. MILLER. The moderator was Dr. C. D. ANDERSON. The third session was on painful syndromes of the upper limb, with Mr. A. MCDOUGALL as moderator and a panel consisting of Professor ROLAND BARNES, Mr. ATHOL R. PARKES, Mr. J. T. BROWN, Mr. T. W HOWAT, Mr. N. J. BLOCKLEY, Mr. D. A. MACPHERSON, and Mr. J. STEVENS. The fourth session was on hiatus hernia and the panel was Professor ILLINGWORTH, Mr. K. FRASER, Mr. W. BURNETT, Dr. J. F. ADAMS, Dr. SCOTT PARK, and Dr. MILLER. Mr. D. H. CLARK was moderator.

Doctors' Hobbies Exhibition

The fourth Doctors' Hobbies Exhibition, sponsored by Benger Laboratories Limited, will be held in the Great Hall of B.M.A. House from December 5 to 9. Many of this year's 470 entrants are doctors who are exhibiting for the first time. There will be some 1,350 items on view, the painting and photography sections again attracting the largest number of entries. Cups will be awarded to the best exhibit in each of the 22 classes. Further prizes will be presented for the three outstanding exhibits in the exhibition.

Medical Research Council of Ireland

In its *Annual Report, 1959*, the Medical Research Council of Ireland welcomes the increased grant from the Minister of Health—an increase from £27,000 on January 1, 1959, to £40,000 a year in October, 1959. The increased funds were used mainly for the support of clinical research. During the year the Council spent £48,485, of which £2,223 went to administration. General research absorbed £13,104, chemotherapy research £22,687, the cell metabolism unit £4,520, and the perinatal mortality study £5,951.

British Diabetic Association

The British Diabetic Association's medical and scientific section met in Glasgow on October 14 and 15. Dr. JØRGEN PEDERSEN, of Copenhagen, was a guest speaker.

The first day was devoted to a colloquium on prediabetes. There were fourteen papers, some of which dealt with genetics, the obstetric aspects, and the role of the thyroid in stress. Two papers described plasma insulin studies, and a further two were on steroid-augmented tests for prediabetes, the one consisting of an intravenous glucose tolerance and the other of glucose excretion in the over-night urine. Light and electron microscopy of the islets of Langerhans of experimental animals treated with growth hormone was described. Tolbutamide appeared to be able to reverse incomplete degenerative changes in the beta cells. The effect of tolbutamide on plasma insulin activity was reviewed, and in the final paper a trial of the sulphonyl-ureas in human prediabetes was suggested. The committee of the section is now planning such a trial. On the second day there was a paper and discussion on the care of elderly diabetics, followed by seven papers on subjects varying from spontaneous diabetes in dogs, quantitative aspects of the endocrine pancreas, and the hypoglycaemic action of salicylate and its analogues, to ballistocardiographic smoking tests in young diabetics.

Herta Oberheuser

A report in *Der Spiegel*, November 9, says that HERTA OBERHEUSER, a doctor who was convicted at the Nuremburg war crimes trial of carrying out experiments on human beings at Ravensbruck concentration camp, is asking the High Court in Schleswig to restrain the Minister of the Interior of Schleswig-Holstein, Herr HELMUT LEMKE, from revoking her licence to practise at Stocksee, near Kiel. Enforcement of this order, which was made in August, 1958, has been obstructed by appeals in various courts. A strong protest was made in 1958 at the B.M.A.'s Annual Representative Meeting against HERTA OBERHEUSER'S return to practice (*Supplement*, July 19, 1958, p. 56) and there was considerable correspondence in the *Journal* on the subject in May, June, July, August, and September of that year.

Edwina Mountbatten Trust

The Edwina Mountbatten Trust in memory of Lady MOUNTBATTEN was formally inaugurated at a reception on November 16 attended by the DUKE OF EDINBURGH, the Trust's patron. The Trust, which hopes eventually to raise £5m., will be used to help the Save the Children Fund, to extend the St. John Ambulance Brigade in Great Britain and the Commonwealth, and to promote and improve the art and practice of nursing. Donations may be addressed to the Edwina Mountbatten Trust, 2 Kinnerton Street, London S.W.1.

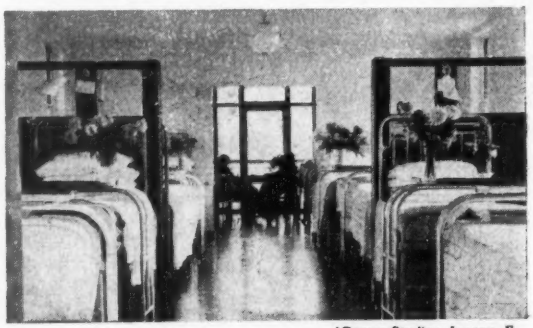
Middlesex Hospital Institute of Clinical Research

On November 22 the clinical research committee of the Middlesex Hospital Medical School entertained visitors to a demonstration of work carried out at the School's Institute of Clinical Research. At the Institute Professor A. KEKWICK, the director, and his colleagues had arranged a visual presentation of their current work. The Wellcome Laboratories were also open for inspection.

New Geriatric Wing, Langthorne Hospital

The DUCHESS OF KENT recently visited Langthorne Hospital, Leytonstone, and opened a new wing for geriatric patients.

There are three floors in the new wing, with ward units on each floor for 20 patients. These units are built in the shape of an L, with ancillary accommodation and the sister's station at the angle of the L. There are five separate four-bed sections in each unit—a flexible arrangement which allows patients in the same clinical category to be nursed together. Meals are served through a hatch from the ward kitchen to the day-room. The day-room has an open fire—a homely amenity which the patients appreciate and which provides a focal point for the community life of the ambulatory patients.



[*Cameo Studios, Leyton, E.*

New Geriatric Wing.

Medical M.P.s' Committee

The following have been elected as officers of the all-party Parliamentary Medical Committee: *chairman*, Sir MALCOLM STODDART-SCOTT (Con.); *vice-chairman*, Dr. R. BENNETT (Con.); *honorary secretary*, Dr. J. DICKSON MABON (Lab.); *honorary treasurer*, Dr. D. JOHNSON (Con.).

Deputy Chief Medical Officer, Ministry of Health

The Minister of Health has appointed Dr. N. M. GOODMAN to be a Deputy Chief Medical Officer of the Ministry from December 1 in succession to Dr. G. E. GODBER.

Dr. Goodman joined the staff of the Ministry of Health as a Medical Officer in 1934 after service in the Army in the first world war, a period in general practice, and service with Surrey County Council. He has had considerable experience of international health work, as a member of the health committee of the League of Nations from 1938 to 1945, director of health in the European Regional Office of U.N.R.R.A. from 1945 to 1947, and director of field services of W.H.O. from 1947 to 1949. Since 1955 he has been Principal Medical Officer particularly concerned with the hospital and local health authority services of the four Metropolitan hospital regions.

"Hospital Visiting"

King Edward's Hospital Fund for London has published a manual, *Hospital Visiting*, which suggests to members of hospital management committees and house committees subjects for inquiry and observation when visiting hospitals (price 2s., post free, from the Fund, 34 King Street, London E.C.2).

Christmas Cards and Seals

The Chest and Heart Association (Tavistock House North, Tavistock Square, London W.C.1) is selling 60 seals for 5s. in aid of its education, research, and welfare programme (EUSton 3012).

"Family Doctor"

The December issue of *Family Doctor* is now available, price 1s. 6d. It includes articles on tuberculosis, by Dr. J. E. GEDDES; on finding the unknown diabetic, by Dr. J. J. A. REID; and the diet of patients with duodenal ulcer, by Dr. R. KEMP.

In Brief

London County Council has authorized the provision, at a cost of £144,000, of 72 new Austin ambulances as replacements for use by the London ambulance service.

Royal Faculty of Physicians and Surgeons, Glasgow

Dr. J. H. WRIGHT has been elected president of the Royal Faculty of Physicians and Surgeons of Glasgow.

People in the News

Mr. P. H. JAYES is to be civil consultant in plastic surgery to the Royal Air Force.

Professor H. V. MORGAN, dean and professor of medicine, Khartum University, has been appointed professor of medicine in the University College of Ghana.

Dr. J. B. GIBSON, lecturer in pathology, Queen's University, Belfast, has been appointed visiting professor of pathology to the Western Reserve University, Cleveland, Ohio.

Dr. PHILIPPE BAUWENS is to be the first holder of the Royal Society of Medicine's Richard Kovacs Prize, awarded triennially for distinguished work in physical medicine.

COMING EVENTS

National Association for Mental Health. — Week-end course, London, "Psychiatry for the General Practitioner," November 25–27. Details from Education Secretary, N.A.M.H., 39 Queen Anne Street, London W.1 (Tel.: WELbeck 1272).

Society for the Study of Human Biology.—One-day symposium, "Recent Developments in the Study of Characters of Anthropological Importance," November 26, 10 a.m., Department of Anatomy, University College, London.

London County Council Public Health Department.—Local meeting on role in mental health service of doctors, hospitals, and local health authorities, December 1, 8.30 p.m., St. Giles' Hospital, St. Giles' Road, London S.E.5. Details from Divisional Medical Officer, L.C.C. Public Health Department, 29 Peckham Road, London S.E.5. (RODney 2121.)

Medical Section, Royal Photographic Society.—"Illustrating Endocrinology," an illustrated survey by Dr. J. H. BRIGGS, December 1, 6.30 p.m., Royal Photographic Society, 16 Princes Gate, London S.W.7.

Institute of Dermatology.—Exhibition, December 1–27, by Dr. B. E. D. COOKE, on "Bullous Lesions Affecting the Oral Mucosa," St. John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London W.C.2.

Worshipful Society of Apothecaries of London, Faculty of History of Medicine and Pharmacy.—Dr. A. H. T. ROBB-SMITH, "The Growth of Knowledge of Functions of Blood," December 2, 5.30 p.m., Apothecaries Hall, Blackfriars Lane, London E.C.4.

Bradshaw Lecture.—Sir STANFORD CADE, "Malignant Melanoma," December 7, 2.30 p.m., at the Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2.

Doctors' Hobbies Exhibition.—December 5: 2.30–7 p.m.; December 6, 7, and 8: 9.30 a.m.–7 p.m.; December 9: 9 a.m.–6 p.m. Great Hall, B.M.A. House, Tavistock Square, London W.C.1.

Chest and Heart Association.—Conference on "Stroke Rehabilitation," B.M.A. House, December 9, 2 p.m. Chairman: Professor C. BRUCE PERRY. Admission by invitation only. Applications to Chest and Heart Association, Tavistock House North, London W.C.1.

British Red Cross Society.—Film première, "Macbeth," to be attended by PRINCESS ALEXANDRA, in aid of Bedfordshire and London region branches of the Society, December 9, 8 p.m., Royal Festival Hall, London S.E.1. Tickets (from 1 to 10 guineas) from Film Première Committee, 14 Grosvenor Crescent, London S.W.1 (BELgravia 5454, Ext. 7), the Festival Hall, or agencies.

Institute of Urology.—Week-end course, "Recent Advances in Urology," December 9–11. For details see advertisement p. 71.

Royal College of Physicians of London.—Conference on "Clinical Aspects of Genetics" to be held at the College on March 17 and 18. Details in advertisement p. 70.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

BRITISH JOURNAL OF OPHTHALMOLOGY

Experimental Trachoma Produced by a West Australian Virus. I. Mann, C. H. Greer, D. Perret, and C. McLean.
Responses of the Intra-Ocular Pressure to Diencephalic Stimulation. J. Gloster.
Evisceration Utilizing an Intrascleral Implant. C. Berens and A. S. Breakey.
Visual Aids for the Partially Sighted. E. Gunstensen.
Experiences with Early Contact Lenses and some of their Later Developments. F. Williamson-Noble.
Did 'Ali ibn 'Isa Use General Anaesthesia in Eye Operations? A. Feigenbaum.
Basilar Embolism. B. Crawford.
Diktyoma. The late K. R. Kesavachar and R. V. Junnarkar.
Buphthalmos over Three Generations. W. E. Heath.
Improved Calibrated Electrodes for Diathermy Operations in Retinal Detachment. M. Madroskiewicz.
Improved Stand for the Donor Eye for Corneal Grafting. M. Luntz.
Reviews.
Notes.

Volume 44, No. 11. (Monthly; £6 annually. With *Ophthalmic Literature* and Index, £9.)

MEDICAL AND BIOLOGICAL ILLUSTRATION

Cushing's Syndrome. J. H. Briggs and G. A. Zampa.
Simple Photogrammetric Methods in Medicine. E. A. Miskin.
Illustration of Fossil Vertebrates. Edwin H. Colbert and Chester Tarka.
Kinelaparography. Kunio Yamakawa.
The Bibliographic Service of the Medical Group of the Royal Photographic Society. J. A. Fairfax-Fozzard and M. A. Message.
Area and Volume Measurements by Random Sampling Methods. A. S. G. Curtis.
Direct Serial Kinemacrography. Ralph Marshall and J. W. May.
Audi Partem Alteram.
Equipment and Methods.
Abstracts.
Book Reviews.
Motion Pictures.
Reports and Proceedings.
Index to Volume X.

Volume X, No. 4. (Quarterly; £3 annually.)

ARCHIVES OF DISEASE IN CHILDHOOD

Histological Changes in the Duodenal Mucosa in Coeliac Disease. Charlotte M. Anderson.
The Value of Galactose Phosphate Determinations in the Treatment of Galactosaemia. V. Schwarz.
Treatment of Encephalotrigeminal Angiomatosis (Sturge-Weber Disease) by Hemispherectomy. M. A. Falconer and R. G. Rushworth.
Comparison of Changes in Serum Proteins During Early Treatment in Kwashiorkor and Marasmus. I Macdonald.
High Protein Feeding in Kwashiorkor. Frank Walt and Michael Hathorn.
The Nature of the Neonatal Pulmonary Hyaline Membrane. R. A. Barter and T. G. Maddison.
Patent Ductus Arteriosus in Infancy. Olive Scott and G. F. Gearty.
Congenital Adenomatoid Malformation of Lung with Pneumothorax. Roy G. Spector, Albert E. Claireaux, and E. Rohan Williams.
Pulmonary Infections in Children with a Partial Thoracic Stomach ("Hiatus Hernia"). I. J. Carré.
The Fate of the Partial Thoracic Stomach ("Hiatus Hernia") in Children. I J. Carré and R. Astley.
The Bacterial Flora of the Stomach and Small Intestine in Children with Intestinal Obstruction. Ruth F. Bishop and Charlotte M. Anderson.
Freeze-dried B.C.G John Lorber and Peggy C. Menneer.
A Case of Osteopetrosis (Albers-Schönberg) with Intercurrent Pneumocystis Pneumonitis. W. Aherne.
Intrauterine Blood Transfer between Uniovular Twins. T. Valaes and S. A. Doxiadis.
Pseudohypoparathyroidism in Infancy. L. S. Taitz.
Subserosal Haematoma of the Ileum. Antonio Gentil Martins.
A Case of Woolly Hair Naevus. P. W. Grant.
Carotid Thrombosis in Childhood. David Mymin.
Book Reviews.

Volume 35, No. 183. (Bi-monthly; £4 4s. annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, November 28

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., Mr. A. L. T. Easton: Surgical Complications of Pregnancy.
MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Large Anatomy Theatre, Manchester University Medical School, 8.30 for 9 p.m., Professor R. E. Lane: Doctor in Industry.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. S. Robson: Renal Excretion of Water in Health and Disease.
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. R. G. Mitchell: Physiopathology of the Allergic State.

Tuesday, November 29

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. L. E. Glynn: Auto-antibodies and Diseases of Connective Tissue.
BUTE MEDICAL SOCIETY.—At Anatomy Lecture Theatre, Bute Medical Building, St. Andrews, Fife, 5.15 p.m., B.M.A. Lecture by Dr. A. A. Mason: Application of Hypnotism in Medicine.
COLLEGE OF GENERAL PRACTITIONERS' EAST LONDON FACULTY.—At Anatomy Theatre, London Hospital Medical College, 8.30 p.m., Pfizer Lecture by Professor J. N. Morris: Epidemiology and Clinical Medicine.
INSTITUTE OF CHILD HEALTH.—5.30 p.m., Dr. G. A. Neligan: Some Physiological Measurements in Newborn Infants.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. C. D. Calnan: Cutaneous Allergy (II).
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Sir Aubrey Lewis: Evaluating Psychiatric Treatment.
LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital Medical School, 8 Hunter Street, W.C., 8 for 8.30 p.m., Dr. Katharine Williams: Some Medical Aspects of Radiation Protection.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., FitzPatrick Lecture by Dr. K. D. Keele: Evolution of Clinical Methods in Medicine—(I) Origins of Clinical Examinations.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor H. B. Stallard: Malignant Melanoma of the Choroid Treated with Radioactive Applicators
ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At Manson Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. M. Tanner: Biometrical Problems in Studies of Human Growth.
ST. ANDREWS UNIVERSITY.—At Physiology Lecture Theatre, 5 p.m., Dr. P. G. Aungle: Electroencephalography—Physiological Basis and Chemical Applications.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, Wright-Fleming Institute, 5 p.m., Mr. Philip Rhodes: Fluid Balance in Obstetrics.
UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, Gower Street, W.C., 5.30 p.m., Inaugural Lecture by Professor A. F. Huxley, F.R.S.: Theories of Muscular Contraction—A Historical Survey.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. F. Swann: Myelography.

Wednesday, November 30

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Cellular naevi and Malignant Melanomata.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. H. Nicholson: Diffuse Interstitial Pulmonary Fibrosis.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 2 p.m., Dr. R. Newton: The Pouch of Douglas
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. J. G. Sandrey: Surgery of Calculi.
LONDON UNIVERSITY.—At Westminster Medical School (Meyerstein Lecture Theatre), 5.30 p.m., Dr. Joseph J. Bunim (Bethesda, U.S.A.): The Interrelationship of the Collagen Diseases.
MANCHESTER MEDICAL SOCIETY.—At Large Anatomy Theatre, Manchester University Medical School, 4 for 4.30 p.m., meeting of Fellows. Dr. M. I. Grossman: Gastro-oesophageal Reflux.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. V. Wynn: Electrolyte Metabolism
QUAKER MEDICAL SOCIETY.—At Friends House, Euston Road, London N.W., 8.30 p.m., Lister Lecture by Dr. Cuthbert E. Dukes: Dr. John Fothergill (1712-1780) and His Medical Contemporaries.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. J. P. Bull: Problem of Domestic Burning Accidents (illustrated).
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE: EDINBURGH BRANCH.—At West Medical Theatre, Edinburgh Royal Infirmary, 5 p.m., Dr. D. Stewart McLaren: Some Nutritional Problems in East Africa.
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Dr. C. C. Forsyth: Bilirubin Metabolism in the Newborn Infant—Exchange Transfusion.

Thursday, December 1

BELMONT HOSPITAL CLINICAL SOCIETY.—8 p.m., Dr. L. M. Franklin: The Psychiatrist and the Family Doctor.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. B. Lennox: Nuclear Sexing and Human Chromosomal Anomalies.
LIVERPOOL MEDICAL INSTITUTION.—Mr. C. B. Sedzimir: Stereotaxic Surgery in the Treatment of Parkinsonism.
NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Mr. G. Platt: Arthroplasty of the Knee.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., FitzPatrick Lecture by Dr. K. D. Keele: Evolution of Clinical Methods in Medicine—(2) Quest for Significant Physical Signs.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of Eggland, 5.30 p.m., Otolaryngology Lecture by Mr. J. Pennybacker: Acoustic Neuroma.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Kettle Memorial Lecture by Professor R. W. Scarff: Proliferative Lesions of the Breast

Friday, December 2

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. B. Mitchell-Heggs: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.
MEDICAL ELECTRONICS DISCUSSION GROUP.—At Institution of Electrical Engineers, Savoy Place, London W.C., 5.30 for 6 p.m., discussion to be opened by Dr. G. H. Byford, Ph.D., and Dr. K. G. Williams: Telemetering Biological Data.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. A. P. Forrest: Hypophysectomy in the Management of Patients with Malignant Disease. (2) 4 p.m., Professor G. A. Smart: Spectrum of Thyroiditis.
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. D. M. Green: Theories of Auto-immune Disease.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Superintendent G. E. Salter (New Scotland Yard): Counter-criminal Methods.

Saturday, December 3

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Lecture Room B, Addenbrooke's Hospital, Cambridge, Symposium on Dermatology: Occupational Disorders of the Skin in East Anglia. *Morning:* 10.30 a.m., Dr. A. J. Rook; 11.30 a.m., Dr. J. B. Lyon; 12.15 p.m., Dr. C. H. Whittle. *Afternoon:* 2.15 p.m., demonstration of clinical cases in out-patient department; 3.30 p.m., discussion and Any Questions?
●CAMBRIDGE UNIVERSITY POSTGRADUATE MEDICAL SCHOOL.—At School of Veterinary Medicine, Madingley Road, Cambridge, Symposium on Disorders and Treatments which alter the Actions of Drugs used by the Anaesthetist. 10.30 a.m. and 11.45 a.m., Dr J. W. Dundee, Disorders which Affect the Course of Anaesthesia; 2.15 p.m., Dr. M. F. T. Yealland, Clinical Aspects, with demonstrations of cases; 3 p.m., Dr. Aileen K. Adams, Drug Treatments prior to Surgery and their possible Effect on Anaesthesia; 4 p.m., Dr. E. F. Edson, Possible Effects of Industrial Chemicals on Drug Responses.
MIDLAND THORACIC SOCIETY.—At Birmingham Medical Institute, 36 Harborne Road, Edgbaston, 3 p.m., Dr. D. A. Heath: Hypertensive Pulmonary Vascular Disease.

Sunday, December 4

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m., Mr. Wallace Black: Common Ear, Nose, and Throat Conditions.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Jackson.—On November 14, 1960, at Central Middlesex Hospital, London N.W., to Eileen (formerly Greenwood), wife of Mr. John W. Jackson, M.Ch., F.R.C.S., a sister for Jennifer and Adam—Jane Elizabeth.
Kirby.—On November 6, 1960, at the Cameron Hospital, West Hartlepool, Co. Durham, to Dr. Kathleen M. and J. R. Kirby of 164 Grange Road, West Hartlepool, a sister for Angus—Marion Catherine.
Moffat.—On November 3, 1960, in Croydon, Surrey, to Audrey (formerly Wride), wife of Dr. Robin J R. Moffat, D.Obst.R.C.O.G., a brother for Pamela and Jeremy—Timothy Julian.

DEATHS

Henderson.—On November 8, 1960, at Rupert Cottage, High Street, Newmarket, Suffolk, Norman Keane Henderson, M.B., Ch.B., LL.B., D.P.H., D.P.M., aged 67.
Jones.—On November 3, 1960, Robert Francis Jones, M.B., B.Ch., of the Mill, Pontrobert, Meifod, Mont., late of Tamworth, Staffs.
Pierret.—On November 6, 1960, Robert Pierret, M.D., F.R.C.P., of 95 Avenue Kleber, Paris, and La Bourboule, Puy de Dôme, France.
Ransome.—On November 4, 1960, in a nursing-home, Folkestone, Kent, Andrew Sidney Ransome, M.B., B.Ch., D.P.H., aged 91.
Robertson.—On November 6, 1960, at his home, Struan, Storrington, Sussex, George Struan Roberston, M.D., late of West Dulwich, London S.E., aged 82.
Scott.—On November 6, 1960, at the White House Nursing Home, Crookham, Hants, John Walter Lennox Scott, C.B., D.S.O., M.R.C.S., L.R.C.P., Major-General, late R.A.M.C., retired, of the Beacon Hotel, Fleet, Hants, aged 77.
Sharp.—On November 3, 1960, Clive Justin Hicks Sharp, *M.C.*, M.B., F.R.C.S.Ed., D.T.M.&H., of 26 Mount Drive, Bedford, aged 68.
Smith.—On November 5, 1960, at Marshfield, Carmen Sylva Road, Llandudno, Caerns, John Robert Fitzroy Smith, M.B., B.Ch., aged 37.
Stirling.—On November 8, 1960, at his home, 2 Craigendoran Avenue, Helensburgh, Dunbartonshire, William Neilson Stirling, L.R.C.P.&S.Ed., L.R.F.P.S., late of East Pakistan.
Thomson.—On November 3, 1960, in Bulawayo General Hospital, Southern Rhodesia, Ian Cowan Thompson, M.B., Ch.B., late of Underbank Hall, Stocksbridge, Yorks.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Absorption of Oral Penicillins

Q.—*I have heard that blood-penicillin levels as high as those following oral penicillin V can be obtained by giving oral penicillin G. What blood-penicillin levels can be obtained with (1) oral penicillin V; (2) oral penicillin G; and (3) intramuscular penicillin G? What dose of each is required and for what length of time is an effective concentration maintained? Is oral penicillin G a suitable treatment in adults if the infection is moderate or severe—e.g., bronchitis or lobar pneumonia?*

A.—The questioner has been misinformed. Penicillin G in the usual formulation is poorly and irregularly absorbed, and the average level attained in the blood is lower than that given by penicillin V. There is a new formulation of penicillin G ("falapen," Duncan, Flockhart and Co.) which is more slowly absorbed, so that a therapeutic concentration is maintained in the blood for much longer (up to 12 hours, according to the few observations hitherto reported), but this concentration is not high, even in the first few hours. The highest blood levels from any oral preparation are those produced by alpha-phenoxyethyl penicillin (phenethicillin, "broxil"), but in the treatment of streptococcal or pneumococcal infections this advantage is neutralized by the lesser activity of this form of penicillin against these organisms. No orally administered penicillin gives concentrations in the blood equalling those produced by the same dose of penicillin G given by injection. For a detailed answer to these questions a recent paper by McCarthy and Finland[1] should be consulted: these authors compared the blood levels produced by all these forms of penicillin in an elaborate and searching series of tests. To obtain a sustained effect oral penicillin (other than the long-acting falapen) should be given at four-hour intervals in doses of 300 mg. (500,000 units). It is a matter of opinion whether such treatment suffices for pneumonia: in an acutely ill patient it is probably better at least to begin with a few doses given by injection.

REFERENCE

[1] McCarthy, C. G., and Finland, M., *New Engl. J. Med.*, 1960, **263**, 315.

Emergency Equipment in Ambulances

Q.—*What emergency surgical equipment should be carried in ambulances in a country area where roads are good and there are up-to-date hospitals? Is there any need to carry chloroform or an intravenous anaesthetic? Should morphia be included, and in what form? Is adrenaline a useful drug to have available? The equipment is for use by a doctor who might be on the spot.*

A.—Briefly, there are four main treatment needs in first aid at the roadside after major injuries. (1) Wound-cover to protect all open wounds from the risk of added infection. (2) A pressure dressing that would adequately control venous or arterial haemorrhage. (3) Some form of temporary immobilization of major fractures. (4) The relief of respiratory obstruction.

The first two needs are adequately met by the Army types of shell, mine, or burns dressings. These are rather massive dressings of various sizes, the last capable of covering a 22 by 18 in. area (55.9 by 45.7 cm.). They could with advantage be carried, sterile in polythene covers, in all ambulances. In addition to preventing added infection, sufficient pressure can be applied to control haemorrhage if these massive dressings are firmly bound on by almost any form of bandage. The same technique can be used to control or relieve such an emergency as an open or sucking pneumothorax.

The third most frequent need is temporarily to immobilize major fractures in order to relieve pain and to avoid further loss of blood during transport. The avoidance of loss of blood by unnecessary movement of even a closed major fracture is an important first-aid consideration. If the journey is a short one between the accident site and a hospital, adequate immobilization can be obtained by binding the upper limb to the body or the lower limb to its intact counterpart by padded triangular bandages. For longer journeys the Thomas's splint is still the best first-aid measure, but its proper application takes up valuable time.

The fourth urgent need is to relieve respiratory obstruction. This can often be most easily achieved by laying the patient in the prone position, when the jaws drop forward, or by holding the jaws forward when the patient is in the supine position. Ambulances could with advantage carry the new Brook airway, but its safe use needs practice in the new technique of mouth-to-mouth breathing.

There is, in my view, no need for ambulances to carry chloroform, intravenous anaesthetics, morphia, or adrenaline. There is no evidence that the last two drugs have any place in the first-aid treatment of haemorrhagic shock, and there is every reason to believe that chloroform, intravenous anaesthetics, morphia, and adrenaline would be much safer carried in the doctor's own equipment and under the doctor's complete control.

Alcohol and Anticoagulants

Q.—*Do patients on long-term anticoagulant therapy have to restrict intake of alcohol, and, if so, does this restriction apply to all forms of alcohol?*

A.—The majority of patients on long-term anticoagulant therapy are relatively easily controlled, and, once they are stabilized, their dose of anticoagulant remains very constant. In such a patient, when a period of difficulty in control occurs, it is not uncommon to find that it has been preceded by a relatively minor deviation from the patient's normal routine. Over-indulgence in alcohol is one of the events which is sometimes incriminated in this respect. For this reason it is advisable to warn patients on long-term anticoagulant therapy against taking large amounts of alcohol, and this caution should apply to all forms of alcohol. Any patient who habitually consumes a lot of alcohol should certainly be advised to restrict his intake. The effects of alcohol on the liver and the well-known sensitivity of patients with liver disease to anticoagulant drugs are sufficient justification for this admonition to be given, and taken, seriously.

Paraplegia in Hodgkin's Disease

Q.—*Can compression paraplegia occur in association with Hodgkin's disease? A patient with Hodgkin's disease has developed signs of compression paraplegia. Myelography suggested a block at D7, but laminectomy disclosed no visible local lesion.*

A.—Compression paraplegia is a well-recognized complication of Hodgkin's disease and may in rare cases be the presenting clinical feature of the condition. The compression is caused by a lymphomatous deposit in the spinal epidural space. This may in some cases apparently be due to spread from paravertebral glands in the mediastinum with infiltration along the nerve roots, or may be associated with involvement of the vertebrae as shown radiologically, but in other patients there is no evidence of spread from adjacent structures. If the patient mentioned had clinical evidence of a progressive spinal cord compression and myelographic evidence of a spinal block, it is certainly surprising that no abnormality was found at laminectomy. Another type of neurological involvement has recently[1,2] been described in Hodgkin's disease: the

development of areas of demyelination without lymphomatous infiltration, but, in the cases so far recorded, these areas have been in the brain and not in the spinal cord. The subject of neurological involvement in the lymphomas has been discussed in a recent monograph.[3]

REFERENCES

[1] Aström, K. E., Mascall, E. L., and Richardson, E. P., *Brain*, 1958, **81**, 93.
[2] Cavanagh, J. B., Greenbaum, D., Marshall, A. H. E., and Rubinstein, L. J., *Lancet*, 1959, **2**, 524.
[3] Williams, H. M., *et al.*, *Neurological Complications of Lymphomas and Leukaemias*, 1959. Thomas, Springfield, Ill.

Napkin-rash

Q.—*Can you suggest a cure for persistent napkin-rash in a 9-months-old baby? Boiling the napkins, a boric acid final rinse, and the use of a silicone barrier cream have all failed.*

A.—The napkin-rash is directly due to the more or less prolonged contact of a wet, urine-soaked napkin with the skin. Damage to the skin occurs more rapidly when the urine is very acid; it also occurs very rapidly if the child has diarrhoea. The ordinary and common cause of a persistent napkin-rash is simply failure to remove the wet napkin sufficiently soon. Many other factors are blamed, of course, and may occasionally be responsible, and it is also possible that the skin of some babies is more sensitive than others. Furthermore, once a severe napkin-rash has developed the skin may break down more easily.

Tannic acid jelly is useful in a bad napkin-rash, applied twice-daily for two or three days, and sodium citrate, sufficient to keep the urine neutral or just alkaline, may help if the urine is in fact very acid. The principal need, however, is to keep the buttocks free from more than transient contact with urine. This entails frequent changing, washing the buttocks with soap and water at each change for a while, and, when feasible, laying the baby to rest without a napkin. The application of zinc and castor-oil ointment or one of the more fancy creams gives the skin a little further protection.

Dermatitis Herpetiformis

Q.—*What is the modern treatment for dermatitis herpetiformis?*

A.—Treatment of the ordinary adult type of dermatitis herpetiformis is by dapsone (diaminodiphenylsulphone). The great majority of patients respond to a dose of 25 or 50 mg. daily, some require more. Side-effects are uncommon and include cyanosis from altered haemoglobin, and, rarely, liver damage. Dermatitis herpetiformis in children and in the elderly is not usually responsive to this treatment.

Draining Subungual Haematomata

Q.—*A small trephine, used for draining subungual haematomata, was used in the casualty department of the Bristol Royal Infirmary about 15 years ago. I should like to have a description of this instrument and to know if it is still in use. Presumably it is in the nature of a dentist's burr. Is drainage of a subungual haematoma a suitable treatment?*

A.—A small trephine, which was a dental burr, was used for draining subungual haematomata in the casualty department of the Bristol Royal Infirmary until about ten years ago. At that time the method of drainage of these haematomata was changed to the use of a cautery or a blunt instrument which was made red hot in a spirit lamp. The reason for the change was that the pressure which it was necessary to use in order to perforate the nail with the burr caused considerable discomfort to the patient. A cautery is the best instrument, but the nursing staff prefer to use a red-hot needle which will just burn through the nail. Drainage of a subungual haematomata is necessary in most cases, because if left it increases the pain and often becomes infected.

Scarring from Pustular Acne

Q.—*What can be done for severe facial scarring in a woman aged 37 due to pustular acne which has been inactive for six months?*

A.—It is unusual for acne vulgaris to be active to the age of 37, and it may be that the diagnosis is not correct. A remission of six months may only be temporary, and this is important in advising on treatment of scarring. Time will effect some improvement, but if activity has ceased and the scarring is severe a plastic surgeon should be consulted to consider dermabrasion.

Plantar Warts and Public Baths

Q.—*Are plantar warts and molluscum contagiosum contagious? If so, what procedure may usefully be taken to prevent spread, especially in public baths?*

A.—Plantar warts and molluscum contagiosum are contagious and due to infective agents, and are spread through public baths. It is difficult to take effective prophylactic measures, but patients affected should avoid public baths. Wearing slippers and careful drying and powdering of the feet affords some protection.

Contact Dermatitis from Wedding Ring

Q.—*A patient of mine can no longer wear her gold wedding ring owing to contact dermatitis developing. Can this ring be lined with some inert transparent plastic material?*

A.—When dermatitis occurs under a wedding ring it is most often due to a domestic cleanser and not to the metal of the ring itself. This occurs because the ring is not removed when wet housework is done, and when the hands are afterwards dried the ring prevents detergents being properly removed from the finger underneath. It would therefore be advisable in this case to make a trial of wearing the ring on another finger and always removing it when the hands are wetted.

Patch tests with the metal of the ring and with other metals might also clarify the situation. If it is shown that sensitivity is to the ring itself, then a coat of plastic inside the ring might well prevent the dermatitis, provided the plastic lining remains complete and free from cracks. Perspex can be dissolved in chloroform and painted on the inside of the ring, a few successive coats being allowed to dry and harden. It would no doubt be necessary to renew this lining periodically. I am not aware that this method of prevention has been used with success, but it is worth trying.

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